ROLE OF MR DIFFUSION WEIGHTED IMAGES (DWI) WITH APPARENT DIFFUSION COEFFICIENT (ADC) VALUES IN NORMAL AND PATHOLOGICAL ENDOMETRIUM

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DECLARATION BY THE CANDIDATE

I hereby declare that the thesis entitled **"ROLE OF MR DIFFUSION WEIGHTED IMAGES (DWI) WITH APPARENT DIFFUSION COEFFICIENT (ADC) VALUES IN NORMAL AND PATHOLOGICAL ENDOMETRIUM"** submitted towards partial fulfillment of the requirements for the award of **MD IN RADIODIAGNOSIS** degree to BFUHS is a compilation of original work carried out by me under the supervision of **Dr. Archana Ahluwalia**, Professor, Department of Radiodiagnosis, **Dr. Ashima Taneja,** Professor & Head Department of Obst. & Gynae & **Dr. Ritu Dhawan Galhotra**, Professor, Department of Radiodiagnosis, Dayanand Medical College and Hospital, Ludhiana. No part of this thesis has formed the basis for the award of any degree previously.

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Dedicated

to

my

Grandparents

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Dr. Navdeep Singh

LIST OF ABBREVIATIONS

ADC	Apparent Diffusion Coefficient
DWI	Diffusion Weighted Imaging
MRI	Magnetic Resonance Imaging
P VALUE	Probability Value
PPV	Positive Predictive Value
NPV	Negative Predictive Value
T1WI	T1 Weighted Imaging
T2WI	T2 Weighted Imaging
US	Ultrasound
EC	Endometrial Carcinoma
PTEN	Phosphatase And Tensin Homolog
HER2	Human Epidermal Growth Receptor 2
HNPCC	Hereditary Non Polyposis Colon Cancer
ET	Endometrial Thickness
ERs	Estrogen Receptors
PRs	Progesterone Receptors
TVUS	Trans Vaginal Ultra Sonography
CT	Computed Tomography
PET	Positron Emission Tomography
FDG	Fluorodeoxyglucose
GdT1WI	Gadolinium T1 Weighted Imaging
DCE	Dynamic Contrast Enhanced
SI	Signal intensity
ROI	Region Of Interest

DW	Diffusion Weighted
FOV	Field Of View
TSE	Turbo Spin Echo

ABSTRACT

INTRODUCTION: Endometrial cancer is the most common gynecologic cancer over 50 years of age. Dense packed tissues with high cellularity such as cancers have relatively little extracellular space which leads to restricted water motion and hence shows lower ADC values than benign and normal tissue.

AIM OF STUDY: To assess the role of MR DWI with ADC values in characterization of endometrium into normal and pathological (benign and malignant) endometrium, and to correlate with histopathological examination wherever possible.

METHOD OF COLLECTION OF DATA: 40 patients with abnormal endometrial thickening on MRI were enrolled in the study. These included 21 malignant endometrial lesions, 11 endometrial hyperplasia and 8 polyps which were proven histopathologically. 30 controls with normal endometrium were included. The mean ADC values of the malignant endometrial lesions, benign endometrial lesions and normal endometrium were recorded.

RESULTS: The mean ADC values ($x10^{-3}$ mm^2/sec) of malignant endometrial lesions, benign endometrial lesions and normal endometrium were 0.75±0.09, 1.50±0.26 and 1.41±0.14 respectively. Statistically significant difference (p-value=0.001) in mean ADC values was found between malignant lesions and benign lesions as well as malignant lesions and normal endometrium. Using 1.03 as a cut off value for distinguishing malignant from benign endometrial lesions, achieved 94.7% sensitivity, 100% specificity, 100% PPV, 95.4% NPV and accuracy of 97.5% with p-value of 0.001. The mean ADC values of endometrial hyperplasia (1.49±0.24) and polyps (1.51±0.29) showed no statistically significant difference. No statistically significant difference in mean ADC values was found between normal endometrium and benign lesions.

CONCLUSION: On the basis of mean ADC values malignant endometrial lesions can be differentiated from benign endometrial lesions and normal endometrium. However, using mean ADC values we cannot differentiated between endometrial hyperplasia and polyp or normal endometrium and benign lesions.

Keywords: DWI, ADC, Endometrial carcinoma, Malignant, Benign

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INTRODUCTION

BACKGROUND

Female gynaecologic conditions arising from the endometrium are common and depend on a women's age, menstrual history, and the use of medications such as hormone replacement and tamoxifen. Both benign and malignant conditions affect the endometrium. Benign conditions must be differentiated from malignant and premalignant conditions. The most commonly used imaging modality for evaluating the endometrium is pelvic ultrasound (US) with transabdominal and transvaginal techniques. Other imaging methods include hysterosonography and magnetic resonance imaging (MRI)[1]. In a woman with postmenopausal bleeding, the endometrium is abnormal if it measures 5 mm or greater and this warrants for endometrial biopsy[2,3]. Some premenopausal women are at increased risk of endometrial carcinoma, and they include women over 35 years of age with morbid obesity, chronic hypertension, chronic diabetes, or long-term tamoxifen therapy. These at-risk patients warrant for endometrial biopsy when there is abnormal vaginal bleeding which is not due to pregnancy and not responsive to hormone therapy and the endometrium measures 16 mm or greater[4,5].

Most of the patients with endometrial pathologies presents with abnormal uterine bleeding. Sometimes endometrial pathologies are asymptomatic and are found incidentally on examination or imaging. Abnormal vaginal bleeding may occur in premenopausal and postmenopausal women. The most common causes of abnormal vaginal bleeding in premenopausal women are hormonal disturbances, fibroids, or adenomyosis and in postmenopausal women are an atrophic endometrium, endometrial hyperplasia, endometrial polyps, endometrial cancer and submucosal fibroids[6]. The most common cause of postmenopausal bleeding is an atrophic endometrium that is diagnosed when the endometrium measures less than 5 mm[2,4].

SPECTRUM OF ENDOMETRIAL PATHOLOGIES

Endometrial cancer [EC] is the most common gynaecologic cancer and approximately 90% of cases occur in women over 50 years of age[7].Endometrial cancer is more common during the 6th and 7th decades of life, with the mean age of patients being 65 years[8]. Histologically, ECs are divided into two subtypes. The most common is the endometrioid adenocarcinoma (type I) that accounts for 90% of the tumours. Type I ECs are associated with oestrogen excess and obesity. These tumours often arise in a background of endometrial hyperplasia, occur in the early postmenopausal period, generally these tumours are low grade, and have a good prognosis. Based on the degree of differentiation, endometrioid adenocarcinomas are subdivided into three grades: Grade 1- well differentiated; grade 2 - moderately differentiated; and grade 3 - poorly differentiated tumours[9]. Type II ECs include the clear-cell, serous papillary subtypes and carcinosarcomas. Type II cancers have no association with oestrogen excess or atypical hyperplasia, generally occur in older women, carry a worse prognosis, and spread like ovarian cancer. All type II cancers and grade 3 endometrioid tumours are classified as high-grade tumours and are associated with a poor prognosis[10]. Recent studies suggest mutations may be present in individual genes such as p53, HER2/neu, and phosphatase and tensin homolog (PTEN) in patients with high-grade endometrial tumours. Mutant tumour suppressor p53 over expression has been associated with poor histological grade, non-endometrioid histology, advanced stage, and poor survival rates[11,12].Positive biomarker, p21, and microsatellite instability have a better prognosis[13] and PTEN mutations are typically associated with more favourable prognosis[14]. HER2/neu proto-oncogene over expression has been associated with poor outcomes in breast, ovary, and endometrial cancer[15] .

Endometrial hyperplasia is a premalignant condition. Both endometrial hyperplasia and cancer are due to unopposed action of oestrogen that may be due to endogenous or exogenous sources,

tamoxifen, obesity, chronic hypertension or diabetes[5]. Endometrial hyperplasia is defined as abnormal proliferation of endometrial glands with increase of gland-to-stroma ratio[16]. The main clinical manifestation of Endometrial hyperplasia is post-menopausal bleeding, although occasionally, patients are asymptomatic. According to the 2014 WHO system classification, Endometrial hyperplasia is classified as endometrial hyperplasia without atypia or atypical hyperplasia/endometrioid intraepithelial neoplasia[17]. Endometrial hyperplasia diagnosis is important due to the higher risk of developing endometrial carcinoma[1].

Endometrial polyps are among the most common pathologic lesions of the uterine corpus[18]. They are benign nodular protrusions of the endometrial surface that consist of irregularly distributed endometrial glands and stroma. They generally consist of three components: (a) a stroma of focally or diffusely dense fibrous or smooth muscle tissue, (b) thick-walled vessels, and (c) endometrial glands[18,19]. Cystic glandular hyperplasia within the polyp occurs most commonly[18,20]. Endometrial polyps may occur with or without generalized endometrial hyperplasia, but polyps are a more common cause of abnormal endometrial thickening than hyperplasia alone[6,21].

RISK FACTORS

Lifestyle disorders like obesity, hypertension and diabetes mellitus are associated with increased risk of endometrial carcinoma. Other risk factors include prolonged oestrogen exposure in form of early menarche or delayed menopause, nulliparity, old age, Stein Leventhal Syndrome, hormone replacement therapy, tamoxifen, and familial cancer syndromes such as HNPCC[22].

Endometrial hyperplasia risk rises with age and is mainly related to chronic endometrial stimulation by oestrogens of both endogenous and exogenous origin[23].

Endometrial polyps are believed to be related to oestrogen stimulation, this may be as a result of an increased concentration of oestrogen receptors (ERs), predominantly ER-alpha in polyp glandular cells compared with normal endometrium, and a decreased expression of progesterone receptors (PRs) A and B in polyps compared with normal endometrium[24,25].

IMAGING TECHNIQUES

Definitive diagnosis of endometrial lesions is made via endometrial biopsy or dilatation and curettage. However, this does not provide information regarding the locoregional spread of disease. The various imaging modalities used to evaluate endometrial carcinoma are described below:

1. Ultrasound

Transvaginal US is often the initial imaging examination for women with dysfunctional (postmenopausal or intermenstrual) uterine bleeding[26]. Increased endometrial thickness is a non-specific finding on grayscale sonography. Endometrial carcinomas typically present as thickening of the endometrium. The sensitivity and specificity of transvaginal ultrasound for detecting endometrial carcinoma is approximately 96% and 61%, respectively, when an endometrial thickness threshold of 5 mm, in postmenopausal women, is used to define abnormal endometrial thickening[27]. Carcinoma is more likely when endometrium has a heterogenous echotexture with irregular and poor outline, while cystic changes are more common in endometrial hyperplasia and polyps. The polyps mostly show pedicle artery sign on doppler evaluation, an uniform echotexture that is isoechoic to the endometrium, an acute angle to the endometrium, an intact endometrial-myometrial interface and smooth margins[28]. Endometrial hyperplasia affects the entire endometrium and results in widening of the endometrium. The endometrial hyperplasia has a cystic lace-like appearance on ultrasound. Myometrial invasion is suggested when a mass disrupts the sub-endometrial halo or extends asymmetrically into

the myometrium[29]. The sensitivity and specificity for TVUS in determining the depth of myometrial invasion are 69% and 70%, respectively[26]. Limitations of TVUS include its operator dependence and limited field of view. In addition, there is insufficient data about the value of TVUS in predicting cervical extension, parametrial invasion, or lymphadenopathy[30].

2. Computed Tomography

On contrast-enhanced CT, endometrial lesions appear as a hypoattenuating and hypo-enhancing masses in the endometrial cavity. Poor soft-tissue differentiation of CT limits its use in the local staging of endometrial carcinoma. The sensitivity and specificity of CT in evaluating myometrial invasion ranges from 40% to 83% and from 42% to 75%, respectively[31]. Currently, CT is used mainly in the assessment of advanced disease, i.e., for staging patients with endometrial carcinoma by detecting nodal and distant metastases.

3. Positron Emission Tomography (PET)

PET-CT depends on the increased metabolic activity of malignant tissue resulting in increased uptake of 18-fluorodeoxyglucose [FDG]. Its role in local tumour staging is limited due to lack of spatial resolution. However, the modality has shown high sensitivity and specificity for predicting pelvic nodal involvement and distant metastatic disease. The sensitivity, specificity, and accuracy of PET/CT in the detection of lymph node metastases based on increased tracer uptake by the lymph node and independent of size were reported as 53%, 99%, and 98%, respectively[32].

Fusion studies with PET-MRI have shown better anatomical resolution with better delineation of local tumour spread. It is a valuable technique for the assessment of the primary tumour and nodal staging in patients with endometrial cancer[33].However, this method requires further evaluation in studies.

4. Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) provides anatomical and functional information about endometrial lesions and is playing an important role in clinical decisions regarding endometrial lesions due to its unique characteristics of non-invasiveness, high soft tissue resolution, and multiple imaging parameters. It is considered the most accurate imaging modality for pre-treatment local staging of endometrial carcinoma.

MR Imaging Appearance of endometrial lesions

On MRI, endometrial carcinoma is usually seen as a hypo to isointense mass on T1-weighted images (T1WI) and shows heterogenous intermediate signal intensity relative to hyperintense normal endometrium on T2-weighted images (T2WI)[34,35].

On dynamic post-contrast images, tumours show delayed enhancement compared to the normal endometrium, and slower enhancement than the myometrium[36]. The presence of uninterrupted enhancement of the subendometrial zone is best evaluated at approximately 25–60s after contrast injection[37]. The maximum contrast between hyperintense myometrium and hypointense endometrial tumour occurs 50–120 seconds after contrast medium administration, and this is the most important phase for accurate assessment of the depth of myometrial invasion[38]. Delayed phase images obtained after 3-4 minutes after contrast injection are useful in detecting cervical stromal invasion[39]. Endometrial carcinoma exhibits impeded diffusion compared with surrounding tissue, manifesting with high signal intensity on high b-value diffusion-weighted MR images and low signal intensity on ADC maps[40,41].

The predominant part of the endometrial polyps (without a central fibrous core or intratumoral cysts) shows slightly low signal intensity on T2WI, the fibrous core appears low-signal-intensity core or stripe on T2WI with intratumoral cysts seen as smooth-walled, variable-sized, well-defined hyperintense cystic structures on T2WI. The polyps

show strong or moderate enhancement on Gd-T1WI. On dynamic MRI, there is early enhancement in the endometrial polyps, which could be used in the differential diagnosis of endometrial carcinomas, because it usually shows weak enhancement on post contrast images and weak early enhancement on dynamic study[42,43].

On MRI, endometrial hyperplasia is iso to hypointense on T2WI as compared to the normal endometrium.

1. Conventional MR Imaging

T2-weighted images (T2WI) can be used to identify the depth of myometrial invasion. However, they often prove inadequate due to poor tumour-myometrium contrast, poor definition of the junctional zone particularly in postmenopausal patients, adenomyosis and leiomyomas that compromise accurate staging. Under these circumstances, DCE MRI and DWI are of particular value.

2. Dynamic Contrast Enhanced MR Imaging (DCE-MRI) DCE-MR imaging is a non-invasive method that allows the evaluation of tumour angiogenesis[22].

DCE-MR enables qualitative and quantitative assessment of tumour status. Semi-quantitative evaluation of DCE-MR images is based on SI changes that can be evaluated using:

- SI curve
- The slope and height of enhancement curve (time-to-peak)
- Maximum SI (peak enhancement)
- Wash-in/ wash-out gradient[22].

Post contrast images are beneficial in the detection of small tumours that may be difficult to define on T2WI. A limitation of this sequence is that some tumours may be isointense relative to the myometrium on the equilibrium phase.

3. Diffusion Weighted MR Imaging (DW-MRI)

DW-MRI is a functional imaging technique that displays information about the extent and direction of random water motion in tissues[45].

DW images should always be reviewed with their corresponding ADC maps to avoid pitfalls such as T2 shine-through (apparent high signal intensity of a lesion due to the long T2).

ADC values are related to the proportion of extracellular and intracellular components within the tissue. Increased tissue cellularity or cell density decreases the ADC measurement. Thus, high ADCs suggest benign processes with low cellularity, whereas low ADCs indicate malignancy with large cell diameter and higher cell density, which restricts water diffusion. Therefore, ADC measurements can be valuable in differentiating benign from malignant lesions[22]. It helps in better depiction of the primary tumour, increasing the detection of local extension in the cervix and skipping metastases to the vagina, and in diagnosing extrauterine spread to the peritoneum and lymph nodes[46].

DWI is particularly useful in patients with nephrogenic systemic fibrosis or patients who have contraindication to intravenous injection of gadolinium-based contrast agents or have tumours that are isointense or hyperintense to the myometrium on contrast-enhanced images[47,48]. DWI is also useful in evaluating the depth of myometrial invasion in the setting of concurrent adenomyosis[49].

AIMS AND OBJECTIVES

To assess the role of MR DWI with ADC values in characterization of endometrium into normal and pathological (benign and malignant) endometrium, and to correlate with histopathological examination wherever possible.

REVIEW OF LITERATURE

Tamai et al [2007] evaluated 18 females with surgically proven endometrial cancer and 12 females with pathologically confirmed normal endometrium in cervical cancer patients. All these cases of endometrial cancer and the normal endometrium appeared hyperintense on DW images. The mean ADC value (10^{-3} mm^2/sec) of endometrial cancer was 0.88 ± 0.16, which was significantly lower ($P < 0.01$) than that of normal endometrium (1.53 ± 0.10). The study concluded that DWI is useful in demonstrating uterine endometrial cancer and ADC measurement has a potential ability to differentiate between normal and cancerous tissue of the endometrium[50].

Fujii et al [2008] retrospectively evaluated 25 uterine endometrial cavity lesions in 25 female patients: endometrial carcinoma (n=11), carcinosarcoma (n=2), submucosal leiomyoma (n=8), and endometrial polyp (n=4). Diffusion weighted images were performed at 1.5 T with b factors of 0–1,000/mm2. The region of interest was defined within the tumour on T2-weighted EPI image and then manually copied to an ADC map. The ADC value was obtained. They compared ADC values between malignant and benign lesions using Student's t-test. The mean and standard deviation of ADC values (10^{-3} mm^2/sec) were as follows: endometrial carcinoma, 0.98±0.21; carcinosarcoma, 0.97±0.02; endometrial polyp, 1.58±0.45and submucosal leiomyoma, 1.37±0.28. The ADC values differed significantly between malignant (0.98±0.19) and benign lesions (1.44±0.34) ($P<0.01$). They defined malignant tumours as cases with an ADC value less than 1.15×10^{-3} mm^2/sec for obtaining the highest accuracy. Sensitivity, specificity, and accuracy were 84.6%, 100%, and 92%, respectively. The study concluded that ADC measurement can provide useful information in differentiating malignant from benign uterine endometrial cavity lesions[41].

Shen et al. (2008) conducted a study to determine the feasibility of diffusion-weighted imaging (DWI) with a single-shot echo-planar sequence and parallel technique for depicting endometrial cancer and to examine the role of this technique in preoperative assessment. A total of 31 patients were recruited for MRI evaluation of suspicious endometrial lesions. The mean apparent diffusion coefficient of endometrial cancer was 0.864 x 10^{-3} mm^2/sec and that of benign endometrial lesions was 1.277 x 10^{-3} mm^2/sec. The diagnostic accuracy for myometrial invasion was 61.9% for DWI and 71.4% for gadolinium enhanced T1-weighted 3D fat-suppressed spoiled gradient-recalled echo images. The study concluded that DWI can differentiate benign from malignant endometrial lesions. DWI also provides valuable information for preoperative evaluation and should be considered part of routine preoperative MRI evaluation for endometrial cancer[51].

Inada et al [2009] evaluated 23 patients, out of which 19 patients were detected as endometrial cancers only on T2-weighted images. In the remaining 4 patients, of whom two had coexisting leiomyoma, no cancer was detected on T2-weighted images. This corresponds to 83% detection sensitivity for the carcinomas. When DW images and fused DW images/T2-weighted images were used in addition to the T2-weighted images, cancers were identified in 3 of the remaining 4 patients in addition to the 19 patients (overall detection sensitivity of 96%). The mean ADC value of endometrial cancer (n=22) was (0.97+/-0.19) x10^{-3} mm^2/sec, which was significantly lower than those of the normal endometrium, myometrium, leiomyoma and adenomyosis ($p<0.05$). The study concluded DWI can be helpful in the detection of uterine endometrial cancer in nonenhanced MRI[52].

Takeuchi et al [2009] evaluated Sixty-seven endometrial lesions including 45 cancers and 22 benign lesions (hyperplasia and polyps) by DWI with apparent diffusion coefficient (ADC) measurement. The

staging accuracies of DWI and gadolinium enhanced T1-weighted images in the assessment of myometrial invasion were evaluated in 33 patients with endometrial cancer. The ADC values ($x10^{-3}$ mm^2/sec) in cancer and benign lesions were 0.84±0.19 and 1.58±0.36, respectively (P<0.01). The staging accuracy (superficial or deep myometrial invasion) was 94% for DWI and 88% for gadolinium-enhanced T1-weighted images. Coexisting adenomyosis and infiltrative myometrial invasion caused staging errors on gadolinium-enhanced T1-weighted images, whereas DWI could demonstrate the tumour extent correctly. The study concluded that DWI provides helpful information in evaluating benign and malignant endometrial lesions[47].

Masroor et al. (2010) conducted study on 52 patients, out of which10 had hyperintense, 40 had hypointense and 2 had isointense endometrium on T2 weighted imaging. On DWI, 42 patients had hyperintense and 10 patients had hypointense endometrium. In comparison, 40 controls had hypointense endometrium on DWI and 12 had hyperintense endometrium. The mean ADC value for abnormal endometrium was 0.730±0.215 $x10^{-3}$ mm^2/sec and of normal endometrium was1.265±0.305 $x10^{-3}$ mm^2/sec($p < 0.001$). The sensitivity for detection of endometrial carcinoma on DWI was 77.77%. False positive cases were found to be due to secretory and hyperplastic endometrium. False negative findings were found in a few cases of adenocarcinoma, endometroid carcinoma and clear cell sarcoma. The study concluded, in patients with suspected endometrial carcinoma, MRI examination utilizing DWI was a sensitive tool in detecting endometrial cancers with significantly lower ADC values for carcinoma in general. Physiological and histopathological variants may be responsible for a few false results[53].

Wang et al. (2010) evaluated study population including 28 women with surgically proven stage IA endometrial carcinoma, 30 women

with stage IA cervical cancer with pathologically confirmed normal endometrium, and 19 women with proven benign diseases of the endometrium with dilation and curettage. All endometrial carcinomas and normal endometrium exhibited high signal intensity on DW images, whereas endometrial hyperplasia and polyp showed a low or intermediate signal intensity compared with normal outer myometrium. The mean (SD) ADC of stage IA endometrial carcinoma was 0.878 ±0.185 $x10^{-3}$ mm^2/sec, which was significantly lower ($p<0.01$) than that of normal endometrium (1.446 ±0.246 $x10^{-3}$ mm^2/sec) and that of benign endometrial lesions (1.637 ±0.178$x10^{-3}$ mm^2/sec) without any overlap. The study concluded that measurements of the ADC values had the potential to quantitatively differentiate stage IA endometrial carcinoma from normal endometrium and benign diseases of the endometrium. We propose adding DW imaging as an adjunct sequence in the routine MR protocol for the assessment of uterine lesions[54].

Bharwani et al. (2011) conducted a study to assess the use of DWI in the assessment of tumour grade in endometrial lesions. 42 endometrial lesions including 23 endometrial cancers and 19 benign lesions were evaluated with DW-MRI. Visual evaluation and the calculation of mean and minimum ADC values were performed and correlated with histology. There was no statistically significant difference between tumour grades. The mean ADC value of endometrial carcinoma (0.97 ± 0.31) was significantly lower than that of benign endometrial pathology (1.50 ± 0.14). The study concluded that tumour mean and minimum ADC values are not useful in differentiating histological tumour grade in endometrial carcinoma. However, mean ADC measurement can provide useful information in differentiating benign from malignant endometrial lesions. This information could be clinically relevant in those patients where pre-operative endometrial sampling is not possible[55].

Rechichi et al. (2011) investigated the differences in ADC values of endometrial cancer from those of normal endometrium and myometrium and whether they vary according to histological tumour grade, the depth of myometrial invasion, or lymph node status. The mean (± SD) ADC value ($x10^{-3}$ mm^2/sec) of endometrial cancer (0.77 ± 0.12) was significantly lower than that of normal endometrium (1.31 ± 0.11, $p < 0.0001$) and normal myometrium (1.52 ± 0.21, $p < 0.0001$). There was no significant difference between ADC values of endometrial cancer tissue in patients with tumour grade 1 (0.79 ± 0.08), grade 2 (0.76 ± 0.14), or grade 3 (0.75 ± 0.12) ($p = 0.67$); in patients with deep (0.77 ± 0.13) and those with superficial (0.76 ± 0.12) myometrial invasion ($p = 0.87$); and in patients with (0.78 ± 0.10) and those without (0.75 ± 0.14) lymph node metastases ($p = 0.64$). The study concluded that ADC values allow normal endometrium to be differentiated from endometrial carcinoma; however, they do not correlate with histological tumour grade, the depth of myometrial invasion, or whether lymph node metastases are present[56].

Kierans et al. [2013] conducted study on 52 patients with an abnormal endometrium on MRI and subsequent pathologic evaluation (35 benign, 17 malignant) were included. Two radiologists (R1, R2) independently evaluated endometrial abnormalities for characteristics on conventional MRI and DWI. The study found significantly higher frequency in malignant abnormalities were: presence of irregularly marginated endometrial lesion (R1: 71% vs. 34%, R2: 94% vs. 26%), irregular endo-myometrial interface on T2WI(R1: 77% vs. 26%, R2: 94% vs. 29%), irregular endo-myometrial interface on post-contrast T1WI(R1: 82% vs. 23%, R2: 88% vs. 20%), increased signal on high b-value DWI(R1: 82% vs. 20%, R2: 94% vs. 20%), decreased ADC (R1: 88 vs. 40%, R2: 94% vs. 20%) (all $p < 0.001$, both readers). Endometrial thickness, presence of any focal endometrial lesion regardless of contour, diameter of endometrial lesion, endometrial heterogeneity on T2WI,

decreased T2 signal, and increased endometrial enhancement, failed to show significant differences between groups (all p ≥ 0.159, both readers). At multivariate analysis, for R1, irregular endo-myometrial interface on post-contrast T1WI and increased DWI signal were significant independent predictors of malignancy (AUC = 0.89); for R2, only increased DWI signal was a significant independent predictor of malignancy (AUC = 0.87). The study concluded, abnormal signal on DWI and irregularity of either the endo-myometrial interface or focal endometrial lesion were the most helpful MRI features in differentiating benign from malignant endometrial abnormalities[57].

Inoue et al. [2013] conducted retrospective study on 63 patients of endometrioid adenocarcinomas. Of the 63 endometrioid adenocarcinomas, 42 were well-differentiated (grade 1), 14 were moderately differentiated (grade 2), and seven were poorly differentiated (grade 3). The minimum ADC was 0.64 103 mm2 /s for grade 1 (G1, n = 42), 0.62 for grade 2 (G2, n = 14), 0.46 for grade 3 (G3, n = 7) on freehand ROI. There were significant differences between G1 and G3 (P = 0.007), and G2 and G3 (= 0.038). No significant correlation was found between tumour grade and mean ADC (0.85 for G1, 0.82 for G2, and 0.72 for G3, P = 0.166). The minimum ADC was significantly lower for patients with deep myometrial invasion (n = 21, 0.54) than for those with superficial (n = 39, 0.65) myometrial invasion. Conversely, mean ADC did not differ significantly (0.84 for superficial and 0.78 for deep myometrial invasion, P = 0.081). The study concluded minimum ADC correlates with prognostic parameters of endometrial carcinoma more strongly than mean ADC. Lower minimum ADC is associated with higher histological tumour grade and higher degree of myometrial invasion[58].

Cavusoglu et al. [2016] enrolled 52 patients to investigate the feasibility of diffusion-weighted magnetic resonance imaging (DWI)

with apparent diffusion coefficient (ADC) values in differentiating endometrial cancer from benign endometrial lesions in postmenopausal patients with vaginal bleeding and endometrial thickening and to predict the depth of myometrial invasion in endometrial cancer. Fifty-two patients (mean age: 57 ± 10, range: 41–79) were enrolled in the study. Thirty-eight of the lesions were benign (27 as hyperplasia/endometritis and 11 as polyps). 14 of the 52 endometrial lesions were pathologically proven as cancers and underwent hysterectomy, and all the specimens were reported as endometrioid adenocarcinomas. The mean ADC value (10^{-3} mm^2/sec) of cancer (0.88 ± 0.10) was significantly lower than that of benign lesions (1.78 ± 0.27, p = 0,001). There was no significant difference between ADC values of endometrial tissue in patients with FIGO stage 1A (0.87 ± 0.11, n = 9) and FIGO stage 1B (0.91 ± 0.07, n = 5). The staging accuracy was 92.9 per cent (13/14) for DWI and 85.7 per cent (12/14) for post contrast T1-weighted images. The study concluded ADC values allow benign endometrial lesions to be differentiated from endometrial cancer in postmenopausal patients but do not correlate with the depth of myometrial invasion and histological tumour grading[59].

Kececi et al. (2016) conducted a study to evaluate the efficacy of diffusion-weighted imaging in differentiating between benign and malignant endometrial lesions and determining tumour grade, also in detection of myometrial invasion depth in malignant lesions. The lesions were classified as benign or malignant according to the histopathological results and, the mean apparent diffusion coefficient 20 (ADC) values were compared. For determining the myometrial invasion depth of malignant lesions, T2W, DWI and dynamic contrast-enhanced T1-weighted images (DCE T1WI) were evaluated individually. The sensitivity, specificity and area under the curve for discriminating between malignant and benign lesions by using cut-off ADC value of 1.10 × $x10^{-3}$ mm^2/sec were 85.7%, 92.8% and 0.95, respectively. According to the histopathological grading,

there was no difference in the mean ADC values. The diagnostic accuracy of MRI in determining the depth of myometrial invasion in malignant lesions was found to be 87.1%, 89.7% and 76.9%, 76.9% for T2WI DWI and DCE T1WI, respectively. The study concluded that DWI and ADC measurements can accurately discriminate endometrial cavity lesions as benign or malignant. T2WI DWI is highly effective in determining the depth of myometrial invasion[60].

Elsammak et al [2017] concluded that DW-MRI is useful in distinguishing malignant from benign endometrial lesions and tumour staging as well. Endometrial malignancies showed significant low ADC values ($0.82 \pm 1.09 \times 10^{-3}$ mm^2/sec) compared to benign lesions ($1.44 \pm 0.15 \times 10^{-3}$ mm^2 /s) (p: 0.000). Using 1.19 103 mm2 /s as cut-off value for distinguishing malignant from benign lesions achieved 88.9% sensitivity and 100% specificity. This study found there was a high sensitivity when using DWI and ADC values in diagnosing endometrial diseases. Also, in addition to conventional MRI adding ADC cut off values has increased the diagnostic accuracy for distinguishing malignant from benign endometrial lesions[61].

Keriakos et al. (2018) conducted a study to assess the ability of DWI in the detection, characterization and staging of uterine tumours. DWIs with ADC maps showed a sensitivity and specificity of 80% in endometrial cancers. The mean ADC value for endometrial cancers was $0.8 \times x10^{-3}$ mm^2/sec. The study concluded that conventional MRI findings in conjunction with DWI and quantitative measurement of the ADC are effective methods in the diagnosis and staging of uterine cancer[62].

Mansour et al [2019] evaluate the role of DWI in the diagnosis and differential diagnosis of benign and malignant focal endometrial masses. The 50 studied lesions were classified according to their

histopathological results into the benign group (28 lesions, 56%) and the malignant group (22 lesions, 44%). Conventional MRI could correctly diagnose 39 of the 50 lesions (22/28 benign and 17/22 malignant lesions), achieving a sensitivity of 77.27%, specificity of 78.56%, accuracy of 78%, predictive positive value (PPV) of 73.91%, and negative positive value (NPV) of 81.48%. By combining DWI and apparent diffusion coefficient (ADC) value mapping at a high b value (b = 1000) in MRI, we could correctly diagnose 47 of the 50 lesions (26/28 benign and 21/22 malignant lesions), with increased sensitivity (95.45%), specificity (92.86%), accuracy (94%), PPV (91.3%), and NPV (96%). Conclusion of this study was that combining DWI with ADC mapping at a high b value in pelvic MRI examination is valuable in differentiating endometrial focal lesions with increased diagnostic sensitivity, specificity, and accuracy[63].

MATERIALS AND METHODS

SOURCE OF DATA

It was a prospective study of patients undergoing Pelvic MRI in Department of Radiodiagnosis, Dayanand medical college and Hospital, Ludhiana over a period of one year from 01 March 2021 to 28 February 2022.

INCLUSION CRITERIA

1. Patients with suspected endometrial pathologies referred for pelvic MRI.
2. Patients referred for pelvic MRI for pathologies other than endometrium as control.

EXCLUSION CRITERIA

1. Patients in which ADC measurement is not possible due to thin endometrium or technical factors.
2. Patients who did not consent to be a part of the study.

METHOD OF COLLECTION OF DATA

40 patients with abnormal endometrial thickening on MRI were enrolled in the study. These included 21 malignant endometrial lesions, 11 endometrial hyperplasia and 8 polyps which were proven histopathologically. 30 controls with normal endometrium were included in the study.

PREPARATION OF PATIENT

Written informed consent was obtained from each patient and relevant detailed history was elicited. Articles such as jewellery, keys, credit cards, watches, coins, and other metallic objects were placed in the provided locker facility. The procedure was explained to the patient in their vernacular language to allay the fear and anxiety. The patients were placed in supine position and had a partially filled bladder. During the entire period of procedure, the

patient was in contact with the technician/doctor by a two-way intercom system.

MAGNETIC RESONANCE IMAGING PROTOCOL

All patients underwent a multiplanar, multi sequential MRI scan of the pelvis on a MAGNETOM SKYRA 48 Channel 3 Tesla MR Machine by Siemens, Germany.

All patients underwent axial T1-weighted, large FOV, axial T2-weighted and sagittal T2-weighted turbo spin echo (TSE) sequences. Thin slice (3mm) axial and coronal oblique T2 weighted TSE sequences (obtained in a plane perpendicular and parallel to the endometrial cavity) were then performed. Axial diffusion weighted images (DWI) were obtained with three b-values (50, 400, 800) reconstructed using extrapolation.

Table 1: MRI Sequence Parameters

Sequences	**Localiser**	**T2 Sagittal**	**T1 Axial**	**T2 Axial**	**T2 Coronal**	**DWI**
Acquisition Time	0:25	3:29	2:55	2:47	2:44	3:22
Orientation	Trans versal	Sagittal	Axial	Axial	Coronal	Axial
Resolution Matrix	179x256	269x384	256x 320	269x384	269x384	114x114
Number of Slices	9	25	25	25	25	25
FoV Read (mm)	420	230	220	220	230	220
FoV Phase (%)	100	100	100	100	100	100
Slice Thickness (mm)	7.0	3.0	3.0	3.0	3.0	3.0
Slice Gap (mm)	7.0	3.1	2.1	2.1	2.1	2.1
Repetition Time (msec)	1000	2800	680	3100	2800	4000
Echo Time (msec)	89	87	18	89	87	64
Flip Angle (deg)	160	180	154	180	175	-
Fat Suppression	None	None	None	None	None	SPAIR
Flow Compensation	No	No	Read	Slice	No	-

MR IMAGE ANALYSIS

All images were analysed for endometrial signal intensity and homogeneity on T1WI and T2WI compared to the adjacent normal myometrium.

The diffusion weighted images were assessed for signal intensity of the diseased / normal endometrium on high b-value (b value = 800 s/mm^2) in axial plane. ADC maps were generated automatically.

For quantitative analysis: The diffusion weighted images were reviewed with the conventional MR images (T2W images) for precise localization of the endometrial lesion. Then ADC values of the diseased endometrium was measured on the ADC map images by placing two regions of interest (ROI) of average size 2-4 mm^2 within the lesion avoiding the areas of fluid or necrosis within the uterine cavity. For controls, two regions of interest (ROI) of average size 2-4 mm^2 were placed in the normal endometrium. We measured two ROIs and used the average value, to reduce random variability in the measurements.

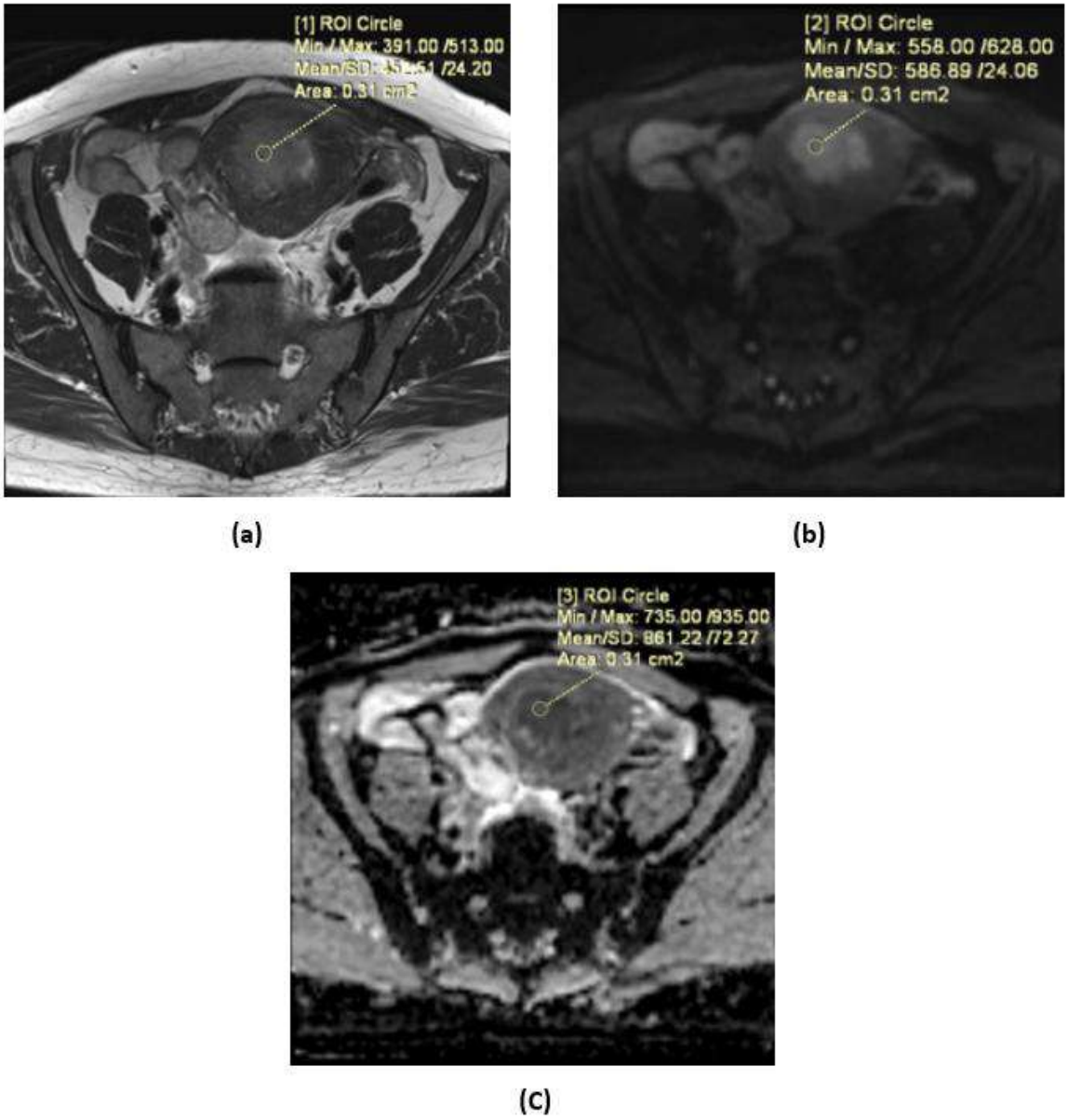


Figure 1: ROI placement for quantitative ADC value

(a) Axial T2-WI, **(b)** DWI and **(c)** ADC images show placement of ROIs in the endometrial lesion.

STATISTICAL ANALYSIS: Data was described in terms of range; mean ± standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Sensitivity, specificity, positive and negative predictive values and accuracy of each MR sequence and their confidence interval (95% CI) were also calculated. Results were analysed using Mann Whitney U test and Kruskal Wallis test for comparison of continuous variables. A probability value (p-value) less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science) 21 version statistical program for Microsoft Windows.

OBSERVATIONS AND RESULTS

1. DEMOGRAPHIC AND CLINICAL DATA

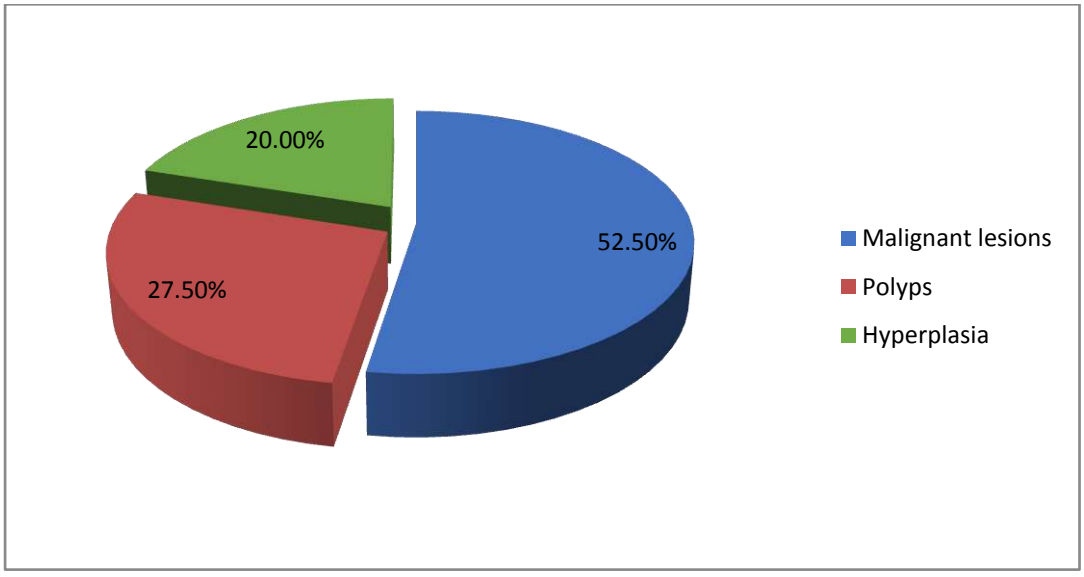
a) Distribution of patients according to pathology

The study included 21 (52.5%) malignant endometrial lesions, 8 (27.5%) hyperplasia and 11 (20.0%) polyps (Table 2, Figure 2).

Table 2: Distribution of patients according to pathology

Endometrial pathology	No. of cases	%Age
Malignant endometrial lesions	21	52.50%
Polyps	11	27.50%
Hyperplasia	8	20.00%
Total	40	100%

Figure 2: Distribution of patients according to pathology



b) Age distribution of cases

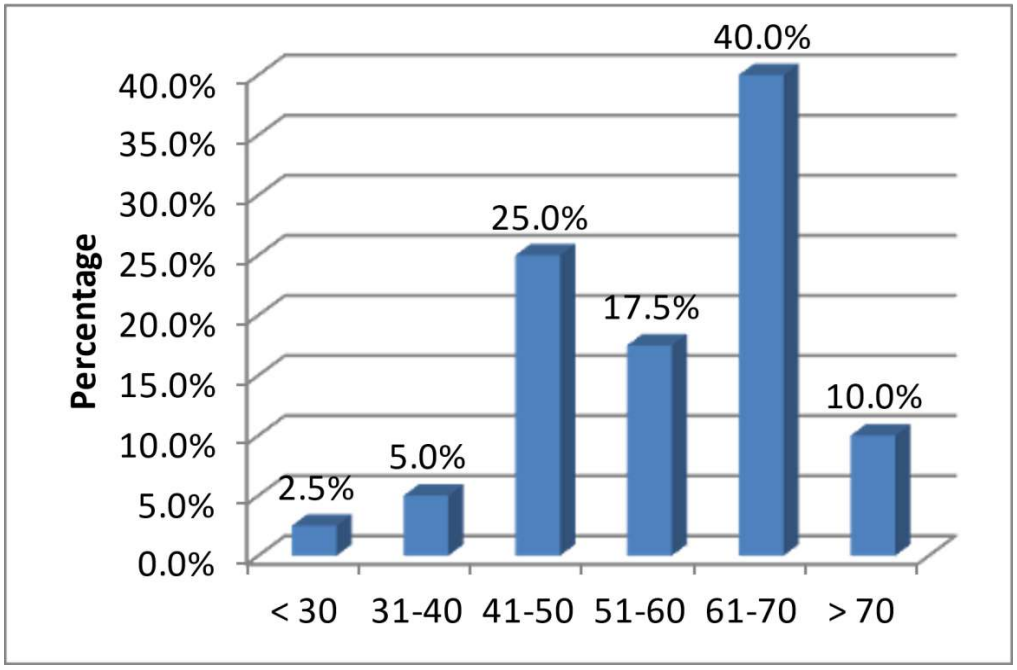
The age range of patients was from 26-82 years with mean age of 58 years.

Out of 40 patients, maximum patients n=16 (40%) in the study were between 61-70 years of age (Table 3, Figure 3).

Table 3: Age distribution of cases

Age group	No. of cases	%Age
< 30	1	2.5%
31-40	2	5.0%
41-50	10	25.0%
51-60	7	17.5%
61-70	16	40.0%
> 70	4	10.0%
Total	40	100.0%

Figure 3: Age distribution of cases



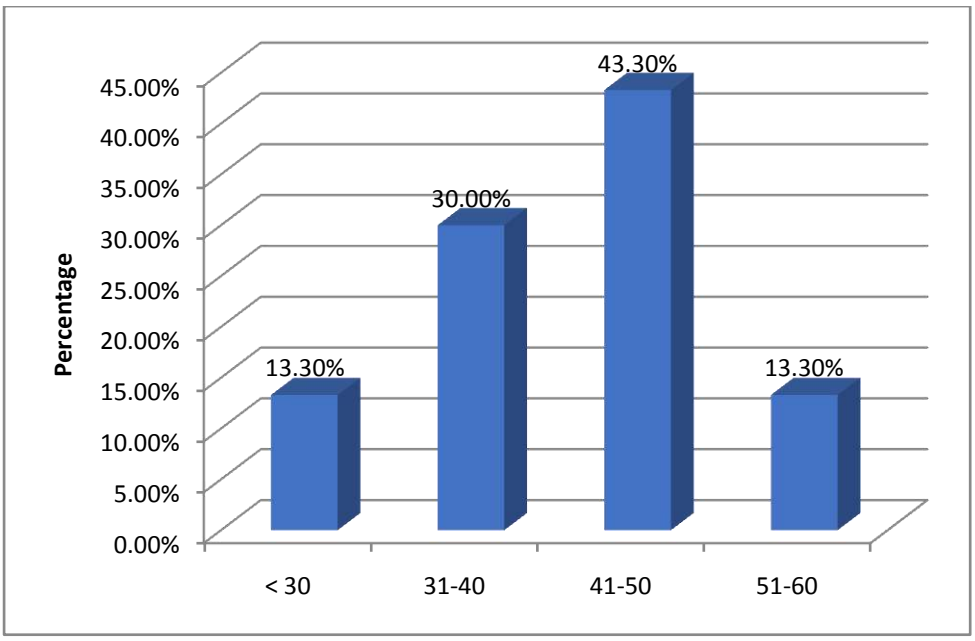
c) Age distribution of controls

30 controls with normal endometrium were included in the study ranging from 26-55 years. Maximum controls n=13 (43.3%) in the study were between 41-50 years of age (Table 4, Figure 4).

Table 4: Age distribution of controls

Age group	No. of cases	%Age
< 30	4	13.3%
31-40	9	30.0%
41-50	13	43.3%
51-60	4	13.3%
Total	30	100.0%

Figure 4: Age distribution of controls



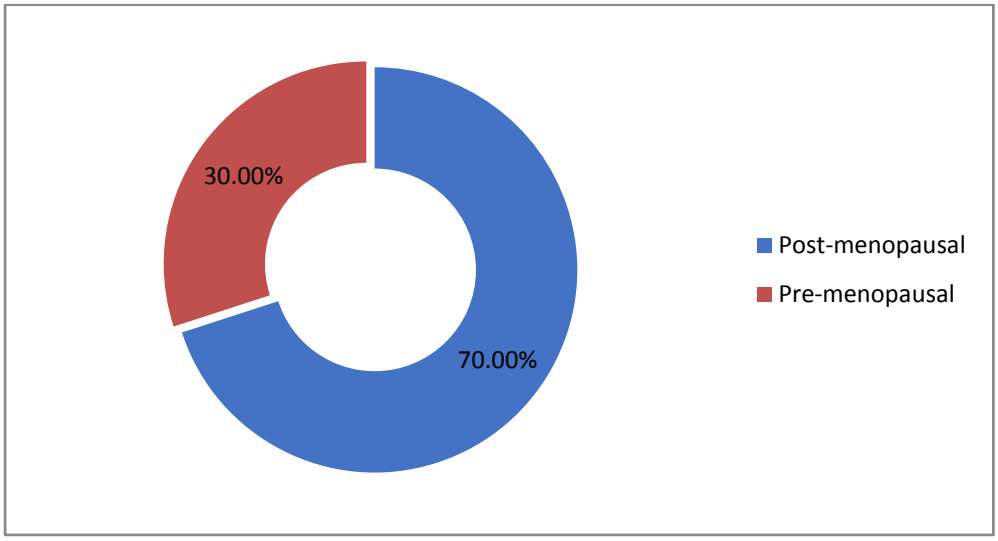
d) Distribution of cases according to menopausal status

28 (70%) patients were post-menopausal and 12 (30%) of patients were pre-menopausal (Table 5, Figure 5).

Table 5: Menopausal status of cases

Menopausal Status	No. of cases	%Age
Post-menopausal	28	70.0%
Pre-menopausal	12	30.0%
Total	40	100.0%

Figure 5: Menopausal status of cases



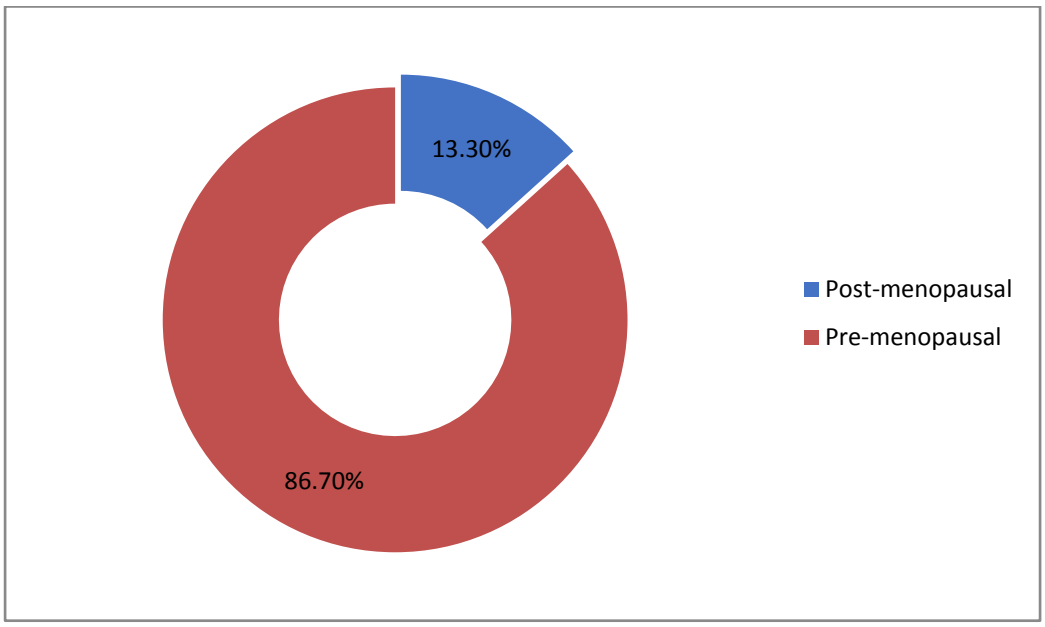
e) Distribution of controls according to menopausal status

Maximum number of controls in the study were pre-menopausal n=26 (86.7%) and n=4 (13.3%) were post-menopausal (Table 6, Figure 6).

Table 6: Menopausal status of controls

Menopausal Status	No. of cases	%Age
Pre-menopausal	26	86.7%
Post-menopausal	4	13.3%
Total	30	100.0%

Figure 6: Menopausal status of controls



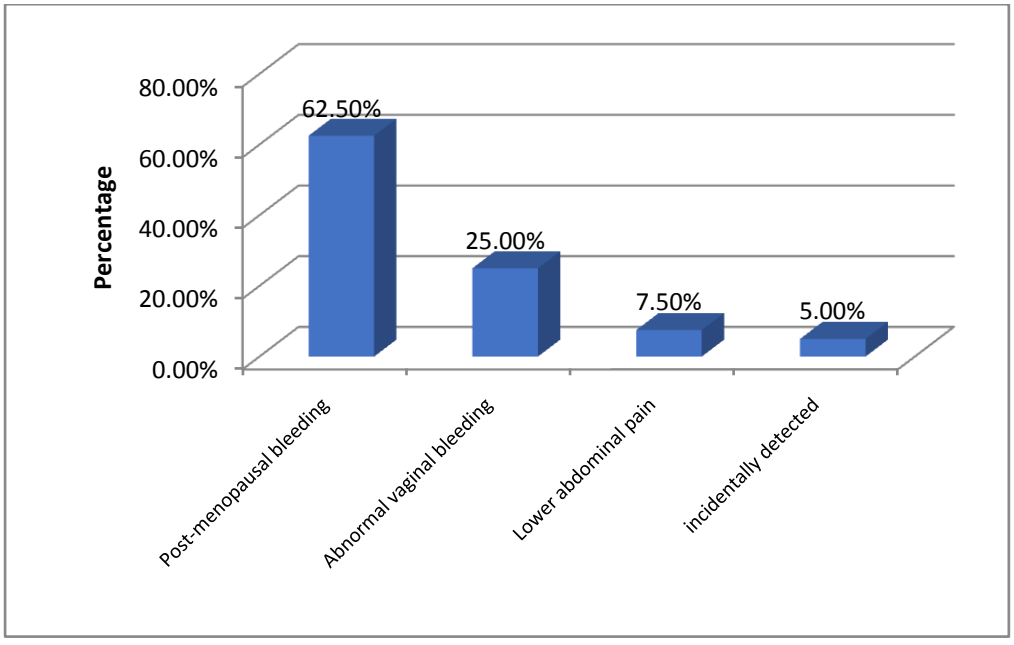
f) Clinical symptoms

The most common presenting symptom was post-menopausal bleeding (n=25, 62.5%). Patients in the pre -menopausal age group presented with abnormal vaginal bleeding (n=10, 25%), 3 (7.5%) patients presented with lower abdominal pain and 2 (5%) post-menopausal patient was incidentally detected with endometrial hyperplasia (Table 7, Figure 7).

Table 7: Distribution of patients according to clinical symptoms

Clinical complaints	No. of cases	%Age
Post-menopausal bleeding	25	62.5%
Abnormal vaginal bleeding in pre-menopausal	10	25.0%
Lower abdominal pain	3	7.5%
incidentally detected	2	5.0%
Total	40	100.0%

Figure 7: Distribution of patients according to clinical symptoms



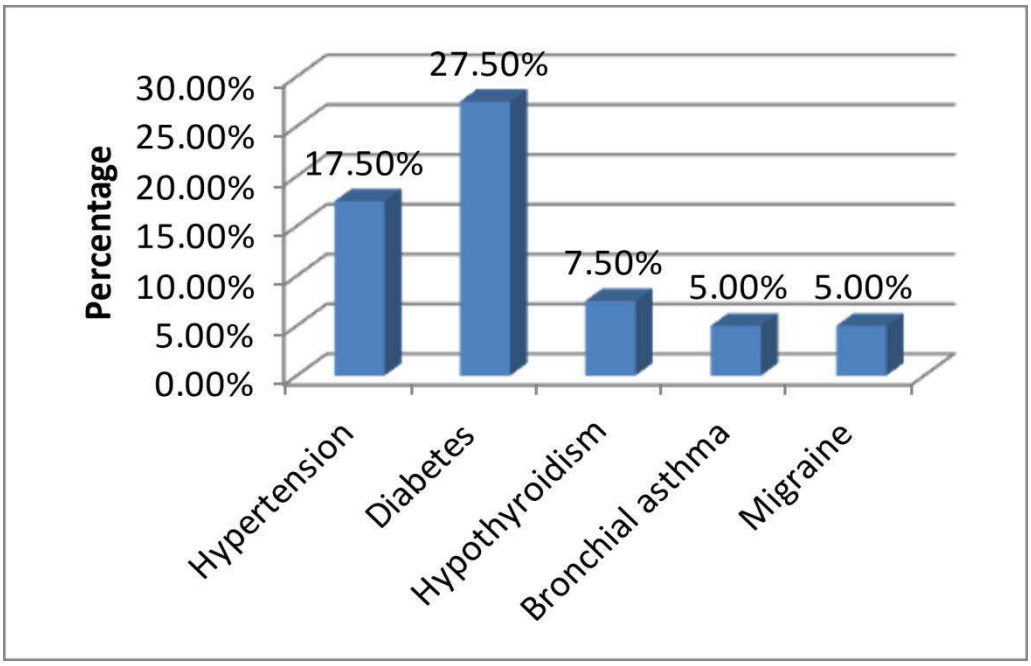
g) Associated co-morbidities

Patients in our study had multiple co-morbidities. Diabetes mellitus as an associated co-morbidity was seen in n=11 (27.5%) patients and hypertension in n=7 (17.5%) patients (Table 8, Figure 8).

Table 8: Associated co-morbidities in the cases

Co-morbidities	No. of cases	Percentage
Hypertension	7	17.5%
Diabetes	11	27.5%
Hypothyroidism	3	7.5%
Bronchial asthma	2	5.0%
Migraine	2	5.0%

Figure 8: Associated co-morbidities in the cases



2. MRI FINDINGS

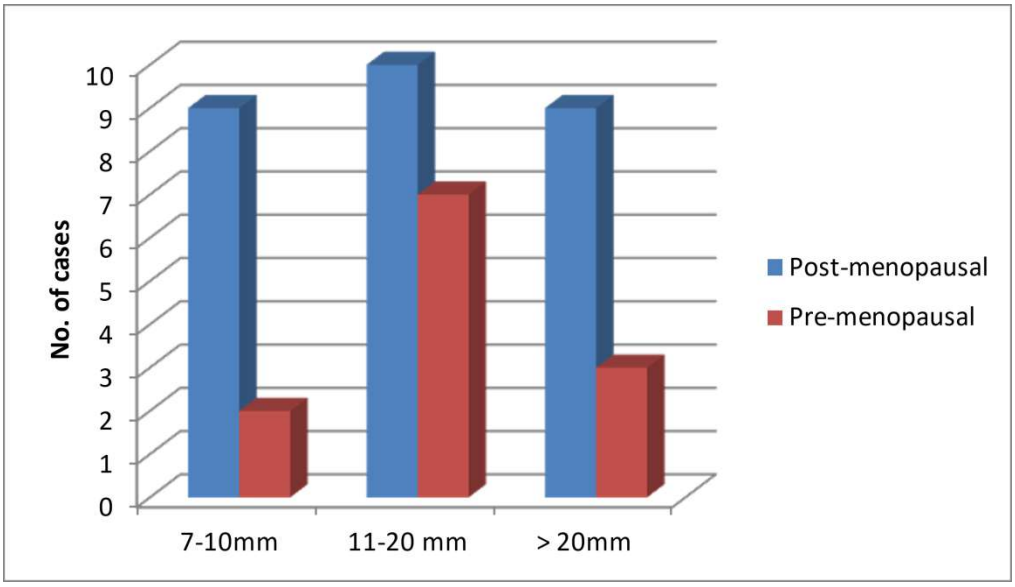
a) Endometrial thickness in cases

Most patient (10 post-menopausal and 7 pre-menopausal =17) had endometrial thickness between 11-20 mm. 9 post-menopausal and 2 pre-menopausal had thickness in the range of 7-10 mm. Endometrial thickness >20 mm was seen in 9 post-menopausal and 3 pre-menopausal patients (Table 9, Figure 9).

Table 9: Endometrial thickness in cases

Endometrial Thickness (mm)	Menopausal Status		Total
	Post-menopausal	Pre-menopausal	
7-10 mm	9	2	11
11-20 mm	10	7	17
> 20 mm	9	3	12
Total	28	12	40

Figure 9: Endometrial thickness in cases



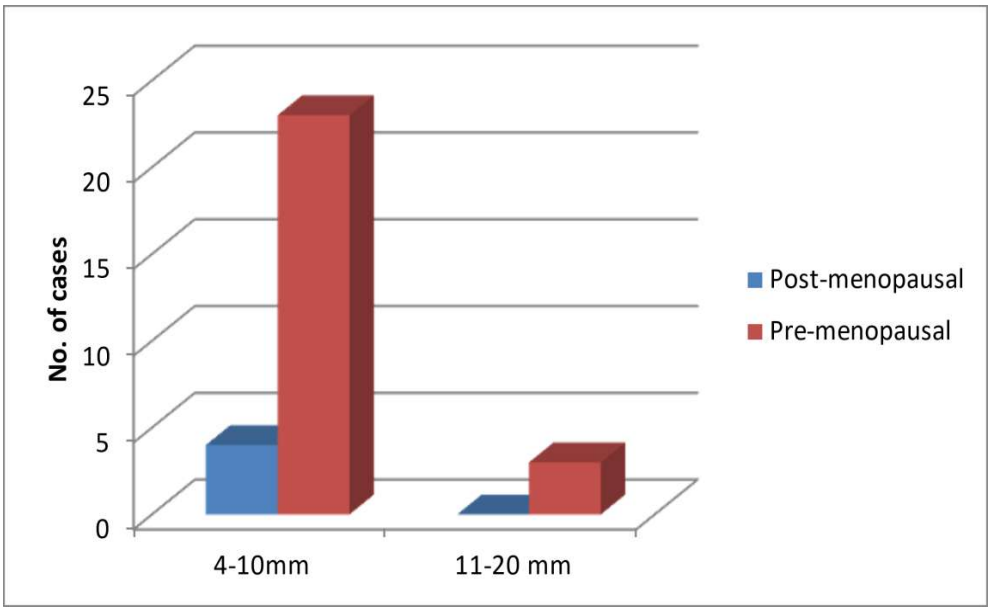
b) Endometrial thickness in controls

Endometrial thickness in the range of 4-10mm was seen in 23 pre-menopausal and 4 post-menopausal patients. 3 pre-menopausal had endometrial thickness in the range of 11-20 mm (Table 10, Figure 10).

Table 10: Endometrial thickness in controls

Endometrial Thickness (mm)	Menopausal Status		Total
	Post-menopausal	Pre-menopausal	
4-10 mm	4	23	27
11-20 mm	0	3	3
Total	4	26	30

Figure 10: Endometrial thickness in controls



c) MR imaging appearance of malignant lesions on T2 weighted images

All malignant endometrial lesions (n=21) were of intermediate signal intensity on T2WI (Table 11).

Table 11: Signal intensity of malignant lesions on T2 weighted images

Signal on T2	No. of cases	%Age
Intermediate	21	100.0%
Total	21	100.0%

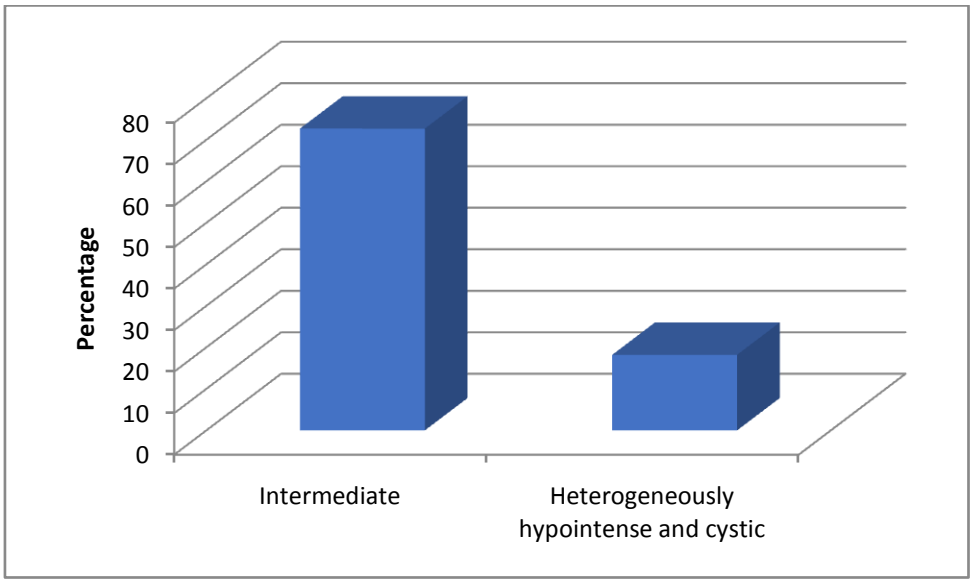
d) MR imaging appearance of benign lesions (polyps and endometrial hyperplasia) on T2 weighted images

8 (72.7%) polyps were of intermediate signal intensity and 3 (27.3%) polyps were heterogeneously hypointense and cystic on T2WI (Table 12, Figure 11).

Table 12: Signal intensity of polyps on T2 weighted images

Signal on T2	No. of cases	%Age
Intermediate	8	72.7%
Heterogeneously hypointense and cystic	3	27.3%
Total	11	100.0%

Figure 11: Signal intensity of polyps on T2 weighted images

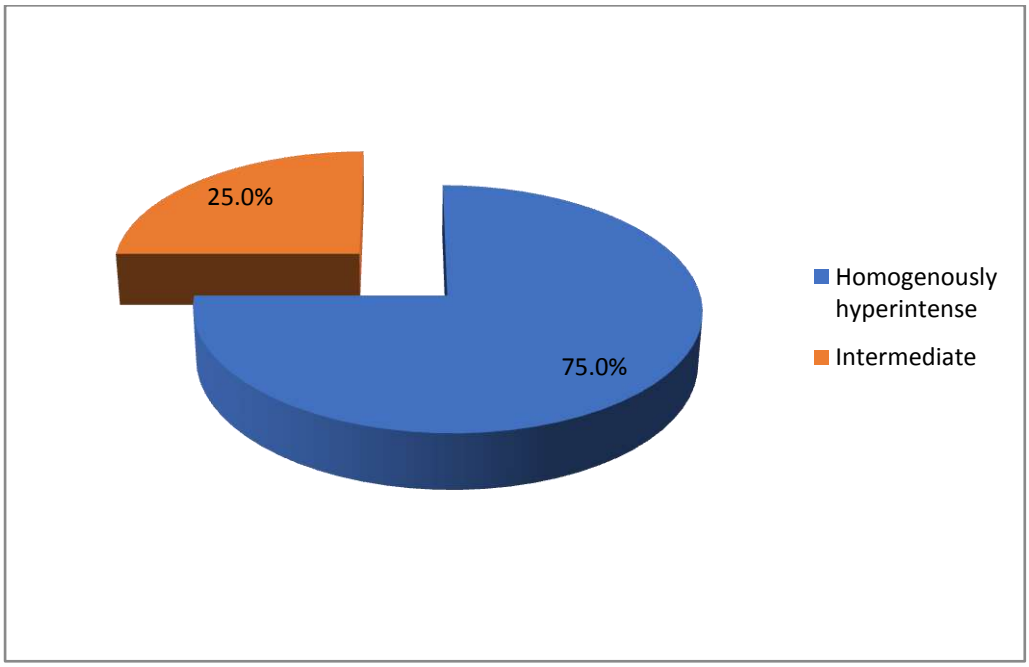


6 (75%) endometrial hyperplasia were homogenously hyperintense and 2 (25%) were of intermediate signal on T2WI (Table 13, Figure 12).

Table 13: Signal intensity of endometrial hyperplasia on T2 weighted images

Signal on T2	No. of cases	%Age
Homogenously hyperintense	6	75.0%
Intermediate	2	25.0%
Total	8	100.0%

Figure 12: Signal intensity of endometrial hyperplasia on T2 weighted images



e) MR imaging appearance of endometrium in controls on T2 weighted images

All controls (n=30) had homogenously hyperintense endometrium on T2WI (Table 14).

Table 14: Signal intensity of endometrium in controls on T2 weighted images

Signal on T2	No. of cases	%Age
Homogenously hyperintense	30	100.0%
Total	30	100.0%

f) MR imaging appearance of malignant endometrial lesions on diffusion weighted images and corresponding apparent diffusion coefficient maps with ADC values

19 (90.5%) malignant endometrial lesions were bright on diffusion weighted images, out of which 18 showed dark signal and 1 showed dark and heterogeneous signal on corresponding ADC maps.

Rest of 2 (9.5%) malignant endometrial lesions showed mixed areas of bright and dark signal on diffusion weighted images with dark and heterogeneous signal on corresponding ADC maps (Table 15, Figure 13, 14).

Table 15: Signal intensity of malignant endometrial lesions on DWI and corresponding ADC maps.

DWI signal	No. of cases (%Age)	Corresponding ADC map signal
Bright	19 (90%)	18 (85.7%) - Dark
		1 (4.8%) - Dark and heterogeneous
Mixed areas of bright and dark	2 (9.5%)	Dark and heterogeneous
Total	21 (100.0%)	

Figure 13: Signal intensity of malignant endometrial lesions on DWI

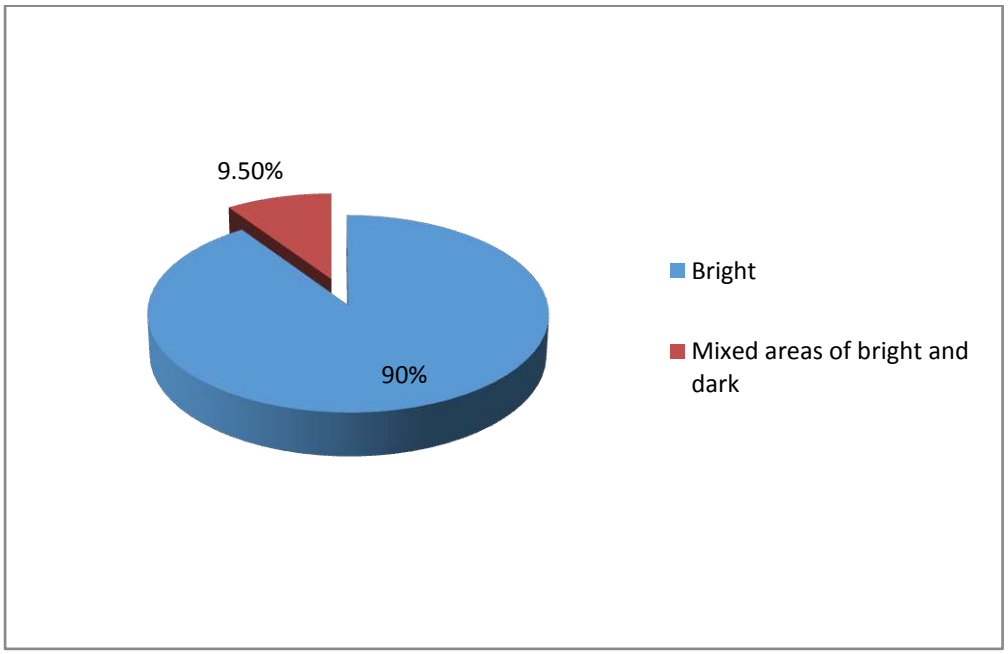
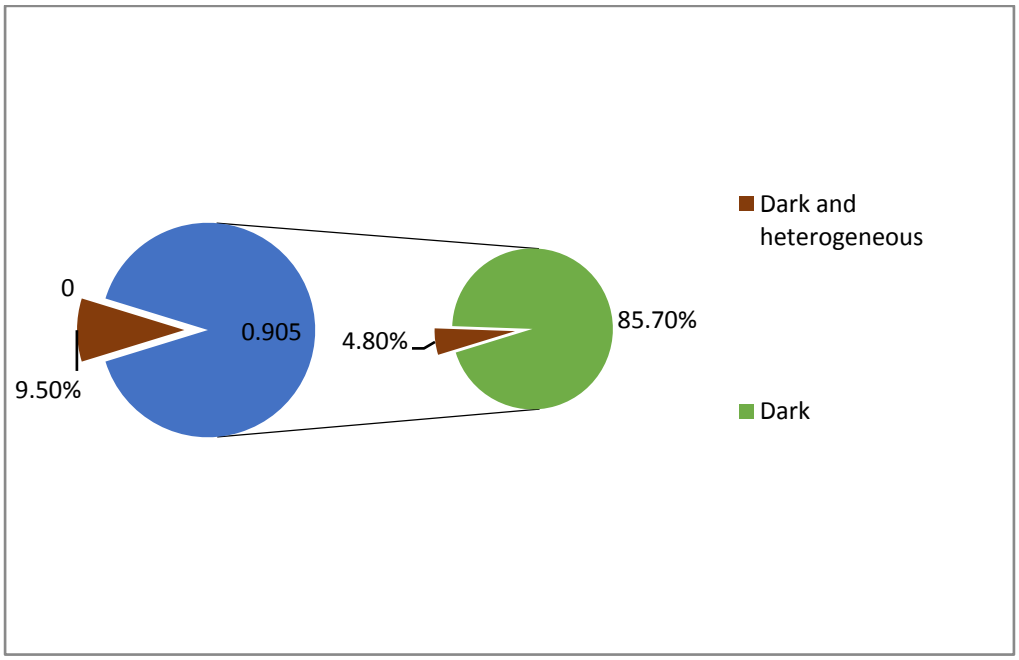


Figure 14: Signal intensity of malignant endometrial lesions on corresponding ADC map



The ADC values of the malignant endometrial lesions ranged between 0.62 - 0.96 x 10^{-3} mm^2/sec with mean ADC of 0.75 ± 0.09 x 10^{-3} mm^2/sec (Table 16).

Table 16: Range and mean ADC values of malignant endometrial lesions

	Range of ADC values (10^{-3} mm^2/sec)	**Mean (± Standard deviation) ADC values (10^{-3} mm^2/sec)**
Malignant endometrial lesions	0.62 - 0.96	0.75 (±0.09)

Most (9) malignant endometrial lesions had ADC values within the range of 0.60-0.70. The second most common range was 0.81-0.90 which had 7 endometrial lesions while 4 lesions were in the range of 0.71-0.80 and 1 lesion was more than 0.90 (Table 17).

Table 17: Distribution of malignant endometrial lesions according to range of ADC values

Range	No. of cases	%Age
0.60-0.70	9	42.9%
0.71-0.80	4	19.0%
0.81-0.90	7	33.3%
> 0.90	1	4.8%
Total	21	100%

g) MR imaging appearance of benign endometrial lesions on diffusion weighted images and corresponding apparent diffusion coefficient maps with ADC values

14 (73.7%) benign endometrial lesions were bright on diffusion weighted images, out of which 13 showed bright signal and 1 showed dark signal on corresponding ADC maps.

4 (21.0%) benign endometrial lesions were dark on diffusion weighted images and showed bright signal on corresponding ADC maps.

And, 1 (5.3%) showed mixed areas of bright and dark signal on diffusion weighted images which was dark signal on corresponding ADC maps (Table 18, Figure 15, 16).

Table 18: Signal intensity of benign endometrial lesions on DWI and on corresponding ADC maps

DWI signal	No. of cases (%Age)	Corresponding ADC map signal
Bright	14 (73.7%)	13 (68.4%) - Bright
		1 (5.3%) - Dark
Dark	4 (21.1%)	Bright
Mixed areas of bright and dark	1 (5.3%)	Dark
Total	19 (100.0%)	

Figure 15: Signal intensity of benign endometrial lesions on DWI

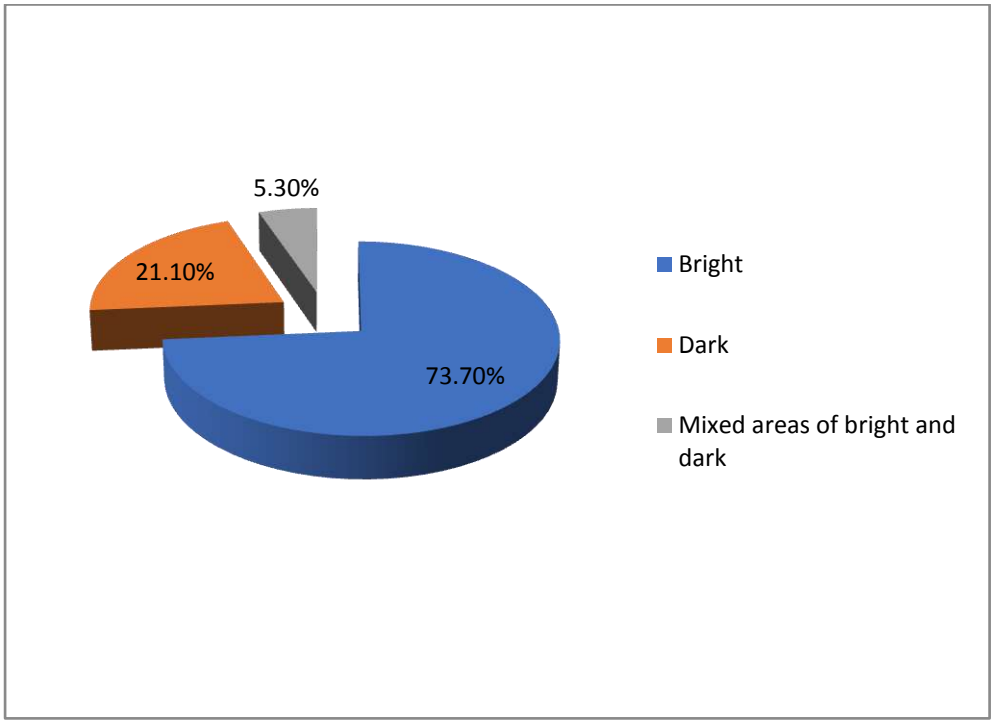
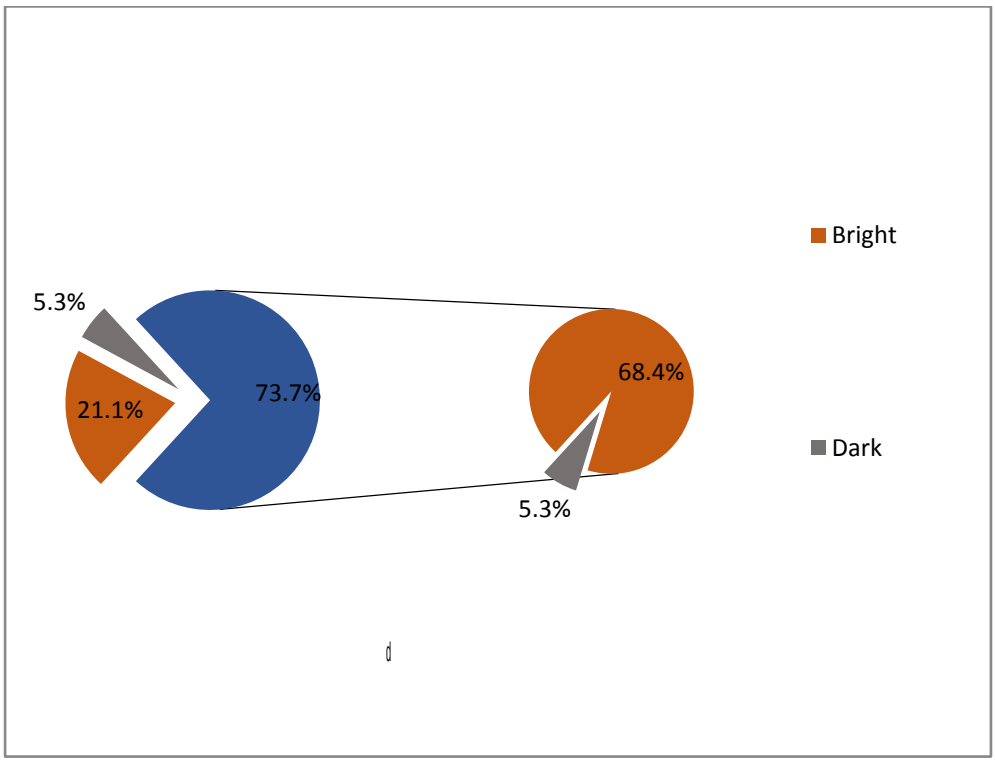


Figure 16: Signal intensity of benign endometrial lesions on corresponding ADC map



The ADC values of the benign endometrial lesions ranged between 1.01 - 1.95 x 10^{-3} mm^2/sec with mean ADC of 1.50 ± 0.26 x 10^{-3} mm^2/sec (Table 19).

Table 19: Range and mean ADC values of benign endometrial lesions

	Range of ADC values (10^{-3} mm^2/sec)	**Mean (± Standard deviation) ADC values (10^{-3} mm^2/sec)**
Benign lesions	1.01 - 1.95	1.50 (±0.26)

Most (6) of the benign endometrial lesions had mean ADC values between 1.4 - 1.6 followed by 4 benign endometrial lesions which had mean ADC values in the range of 1.0 - 1.2. Another 4 benign endometrial lesions had mean ADC values in the range of 1.6 - 1.8 while 3 were within the range of 1.8 - 2.0 and 2 were in the range of 1.2 - 1.4 (Table 20).

Table 20: Distribution of benign endometrial lesions according to range of ADC values

Range	No. of cases	%Age
1.0 - 1.2	4	21.1%
1.2 - 1.4	2	10.5%
1.4 - 1.6	6	31.6%
1.6 - 1.8	4	21.1%
1.8 - 2.0	3	15.8%
Total	19	100.0%

h) MR imaging appearance of endometrial polyps on diffusion weighted images and corresponding apparent diffusion coefficient maps with ADC values

6 (54.5%) polyps were bright on diffusion weighted images, out of which 5 showed bright signal and 1 showed dark signal on corresponding ADC maps.

4 (36.4%) cases were dark on diffusion weighted image sand showed bright signal on corresponding ADC maps.

And, 1(9.1%) showed mixed areas of bright and dark signal on diffusion weighted images which was dark signal on corresponding ADC maps (Table 21, Figure 17, 18).

Table 21: Signal intensity of endometrial polyps on DWI and corresponding ADC maps

DWI signal	No. of cases (%Age)	Corresponding ADC map signal
Bright	6 (54.5%)	5 (45.5%) - Bright
		1 (9.1%) - Dark
Dark	4 (36.4%)	Bright
Mixed areas of bright and dark	1 (9.1%)	Dark
Total	11 (100.0%)	

Figure 17: Signal intensity of endometrial polyps on DWI

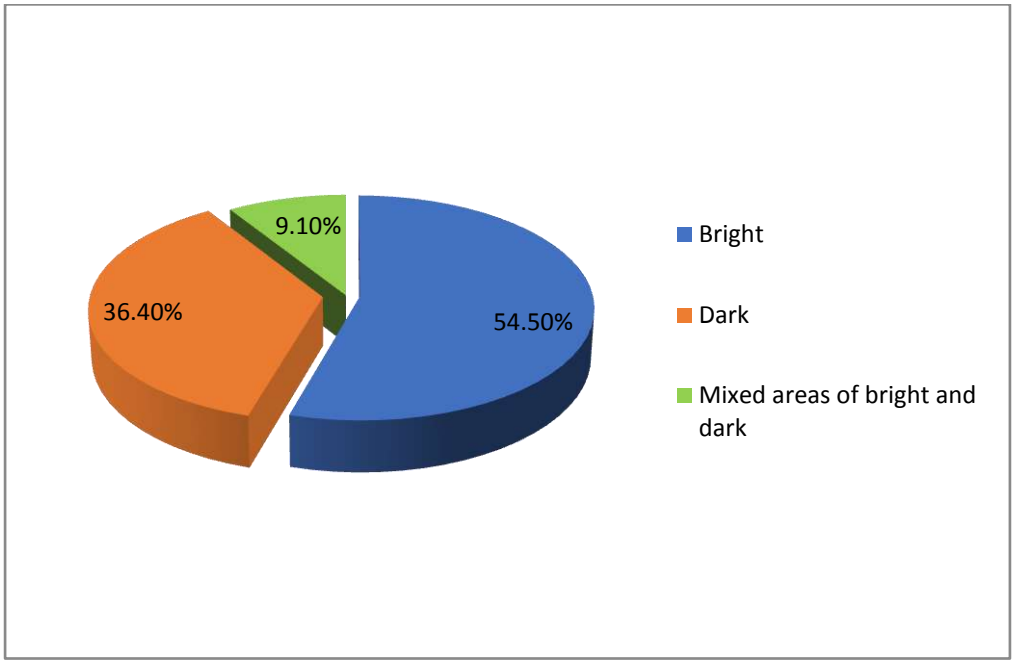
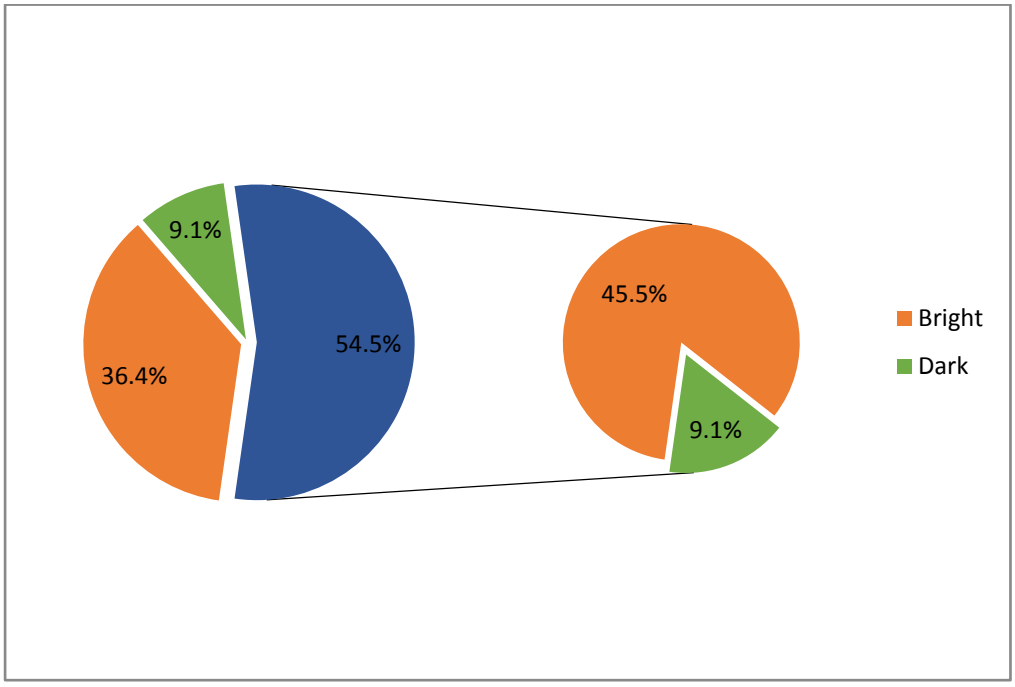


Figure 18: Signal intensity of endometrial polyps on corresponding ADC map



The ADC values of the endometrial polyps ranged between 1.01 – 1.90 x 10^{-3} mm^2/sec with mean ADC of 1.51 ± 0.29 x 10^{-3} mm^2/sec (Table 22).

Table 22: Range and mean ADC values of polyps

	Range of ADC values (10^{-3} mm^2/sec)	**Mean (± Standard deviation) ADC values (10^{-3} mm^2/sec)**
Polyps	1.01 - 1.90	1.51 ± 0.29

Most (5) of the polyps had ADC values within the range of 1.6-1.9 while the ranges 1.0- 1.3 and 1.3 - 1.6 had the same number of polyps which were 3 (Table 23).

Table 23: Distribution of polyps according to range of ADC values

Range	**No. of cases**	**%Age**
1.0-1.3	3	27.3%
1.3-1.6	3	27.3%
1.6-1.9	5	45.4%
Total	11	100.0%

i) MR imaging appearance of endometrial hyperplasia on diffusion weighted images and corresponding apparent diffusion coefficient maps with ADC values

All endometrial hyperplasia (n=8) showed bright signal on both diffusion weighted images and corresponding ADC maps (Table 24).

Table 24: Signal intensity of endometrial hyperplasia on DWI and corresponding ADC maps.

No. of cases (%Age)	**DWI signal**	**Corresponding ADC map signal**
8 (100%)	Bright	Bright

The ADC values of the endometrial hyperplasia ranged between 1.24 - 1.95 x 10^{-3} mm^2/sec with mean ADC of 1.49 ± 0.24 x 10^{-3} mm^2/sec (Table 25).

Table 25: Range and mean ADC values of endometrial hyperplasia

	Range of ADC values (10^{-3} mm^2/sec)	**Mean (± Standard deviation) ADC values (10^{-3} mm^2/sec)**
Endometrial hyperplasia	1.24 - 1.95	1.49 ± 0.24

Most (4) of the endometrial hyperplasia had ADC values within the range of 1.3 - 1.6 while the ranges 1.0 - 1.3 and 1.6 - 1.9 had 2 cases each (Table 26).

Table 26: Distribution of endometrial hyperplasia according to range of ADC values

Range	No. of cases	%Age
1.0-1.3	2	25.0%
1.3-1.6	4	50.0%
1.6-1.9	2	25.0%
Total	8	100.0%

j) MR imaging appearance of normal endometrium in controls on diffusion weighted images and corresponding apparent diffusion coefficient maps

All controls (30) had bright endometrium on both diffusion weighted images and corresponding ADC maps (Table 27).

Table 27: Signal intensity of normal endometrium in controls on DWI and corresponding ADC maps.

No. of cases (%Age)	DWI signal	Corresponding ADC map signal
8 (100%)	Bright	Bright

The ADC values of the normal endometrium ranged between 1.17 - 1.88 x 10^{-3} mm^2/sec with mean ADC of 1.41 ± 0.14 x 10^{-3} mm^2/sec (Table 28).

Table 28: Range and mean ADC values of normal endometrium in controls

	Range of ADC values (10^{-3} mm^2/sec)	Mean (± Standard deviation) ADC values (10^{-3} mm^2/sec)
Normal endometrium	1.17 - 1.88	1.41 (± 0.14)

Most (10) of the controls had ADC values within the range of 1.3 - 1.4. Followed by 8 controls which had ADC values in the range of 1.4 - 1.5 while 6 controls had ADC values more than 1.5 and 4 controls had ADC values in the range of 1.2 - 1.3. Only 2 controls were in the range of 1.1 - 1.2 (Table 29).

Table 29: Distribution of controls according to range of ADC values

Range	No. of controls	%Age
1.1-1.2	2	6.7%
1.2-1.3	4	13.3%
1.3-1.4	10	33.3%
1.4-1.5	8	26.7%
> 1.5	6	20.0%
Total	30	100.0%

k) Statistical analysis of difference in ADC values of malignant endometrial lesions, benign endometrial lesions and normal endometrium

The mean ADC value of malignant endometrial lesions (0.75 ± 0.09 x 10^{-3} mm^2/sec) was on lower side as compared to benign endometrial lesions (1.50 ± 0.26 x 10^{-3} mm^2/sec) and normal endometrium (1.41 ± 0.14 x 10^{-3} mm^2/sec) with statistically significant p-value of 0.001 (Table 30, Figure 19, 20).

Table 30: Range and mean ADC values of malignant endometrial lesions, benign endometrial lesions and normal endometrium

	Range of ADC values (10^{-3} mm^2/sec)	**Mean (± Standard deviation) ADC values (10^{-3} mm^2/sec)**
Malignant endometrial lesions	0.62 - 0.96	0.75 (± 0.09)
Benign endometrial lesions	1.01 - 1.95	1.50 (± 0.26)
Normal endometrium	1.17 - 1.88	1.41 (± 0.14)

Figure 19: Mean ADC values of malignant endometrial lesions, benign endometrial lesions and normal endometrium

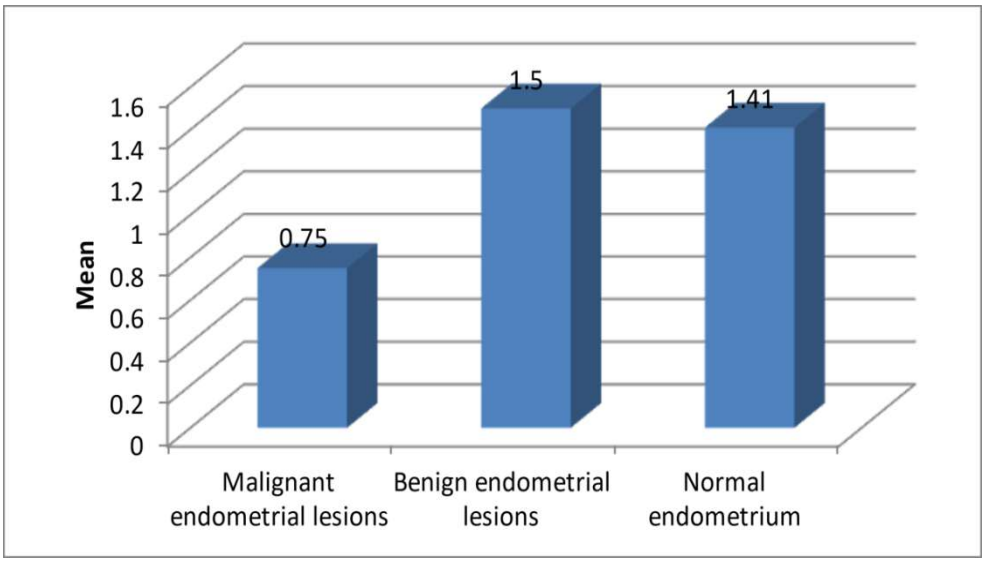
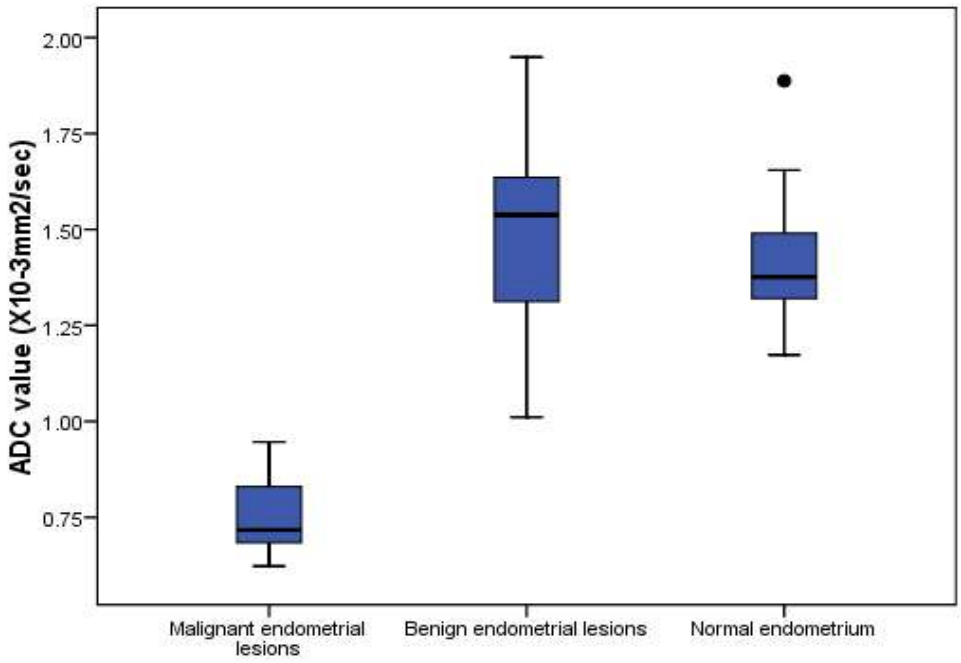


Figure 20: Box and Whisker plot showing ADC values of malignant endometrial lesions, benign endometrial lesions and normal endometrium



l) Statistical values of ADC value cut off to differentiate between malignant endometrial lesions from benign endometrial lesions

Using ADC value of 1.03 x 10^{-3} mm^2/sec as a cut off to differentiate between malignant endometrial lesions from benign endometrial lesions achieved the 94.7% sensitivity, 100% specificity, 100% positive predictive value, 95.4% negative predictive, 97.5% accuracy and p-value of 0.001 (Table 31).

Table 31: Statistical values to differentiate between malignant endometrial lesions from benign endometrial lesions while using cut off ADC value of 1.03 x 10^{-3} mm^2/sec

Statistic	Value	95% CI
Sensitivity	94.74%	73.97% to 99.87%
Specificity	100.00%	83.89% to 100.00%
Negative Likelihood Ratio	0.05	0.01 to 0.35
Positive Predictive Value (*)	100.00%	-
Negative Predictive Value (*)	95.45%	75.71% to 99.30%
Accuracy (*)	97.50%	86.84% to 99.94%

m) Statistical analysis of difference in mean ADC values among benign endometrial lesions i.e., polyps and endometrial hyperplasia

The mean ADC values of polyps and endometrial hyperplasia were 1.51 ± 0.29 x 10^{-3} mm^2/sec and 1.49 ± 0.24 x 10^{-3} mm^2/sec respectively. No statistically significant difference in mean ADC values among benign endometrial lesions i.e., polyps and endometrial hyperplasia was recorded (Table 32, Figure 21, 22).

Table 32: Range and mean ADC values of polyps and endometrial hyperplasia

	Range of ADC values (10^{-3} mm^2/sec)	**Mean ± Standard deviation ADC values (10^{-3} mm^2/sec)**
Polyps	1.01 - 1.90	1.51 ± 0.29
Endometrial hyperplasia	1.24 - 1.95	1.49 ± 0.24

Figure 21: Mean ADC values of endometrial polyps and hyperplasia

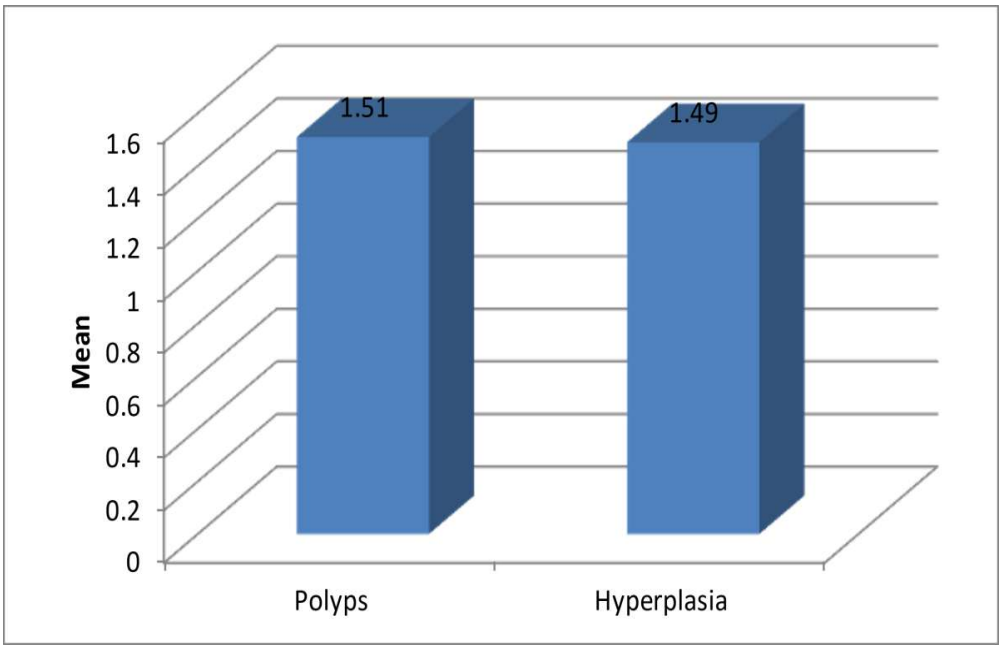
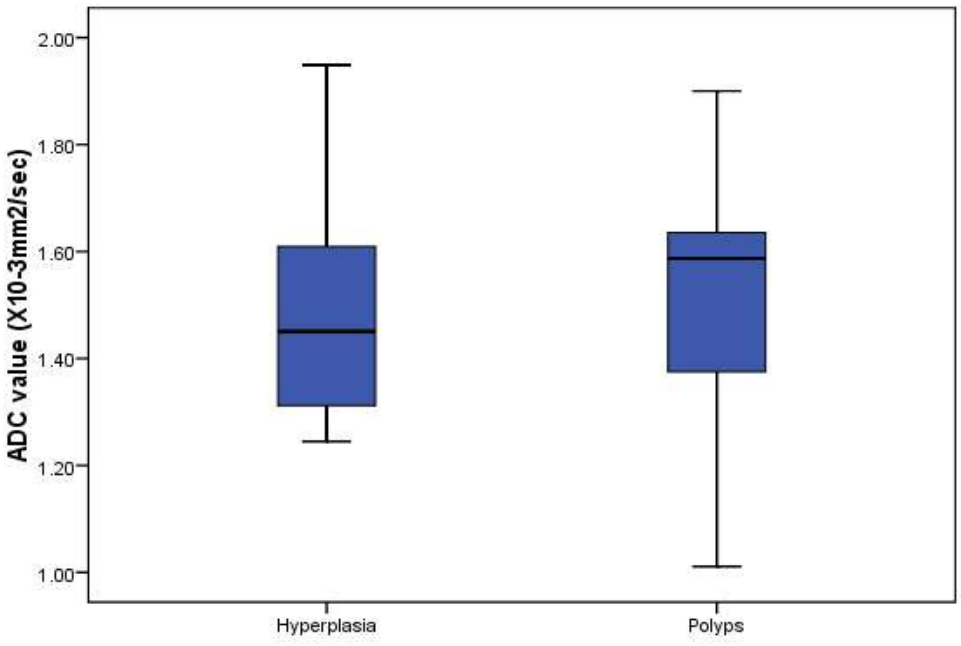


Figure 22: Box and Whisker plot showing ADC values of endometrial hyperplasia and polyps



n) Statistical analysis of difference in mean ADC values of normal endometrium and benign endometrial lesions

The mean ADC values of normal endometrium and benign endometrial lesions were 1.41 ± 0.14 x 10^{-3} mm^2/sec and 1.50 ± 0.26 x 10^{-3} mm^2/sec respectively. No statistically significant difference in mean ADC values of normal endometrium and benign endometrial lesions was recorded (Table 33, Figure 23, 24).

Table 33: Range and mean ADC values of normal endometrium and benign endometrial lesions

	Range of ADC values (10^{-3} mm^2/sec)	**Mean (± Standard deviation) ADC values (10^{-3} mm^2/sec)**
Normal endometrium	1.17 - 1.88	1.41 (±0.14)
Benign endometrial lesions	1.01 - 1.95	1.50 (±0.26)

Figure 23: Mean ADC values of normal endometrium and benign endometrial lesions

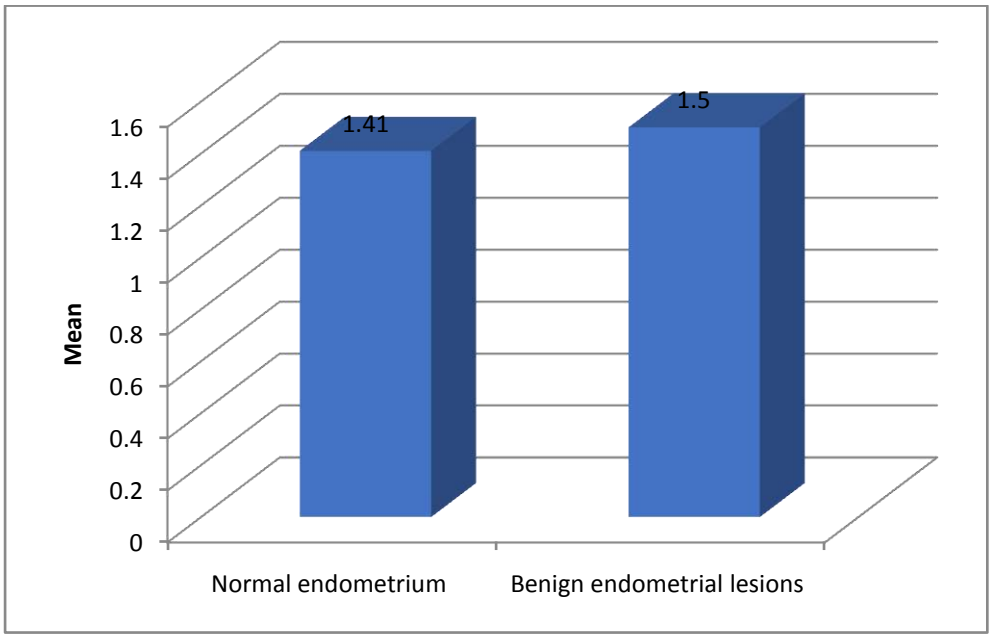
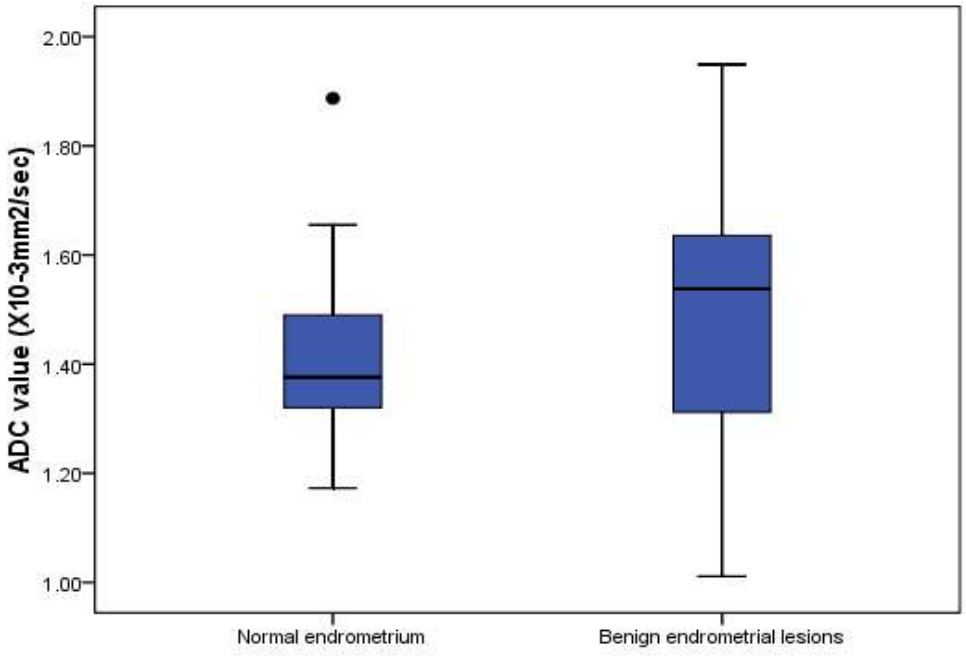


Figure 24: Box and Whisker plot showing ADC values of normal endometrium and benign endometrial lesions



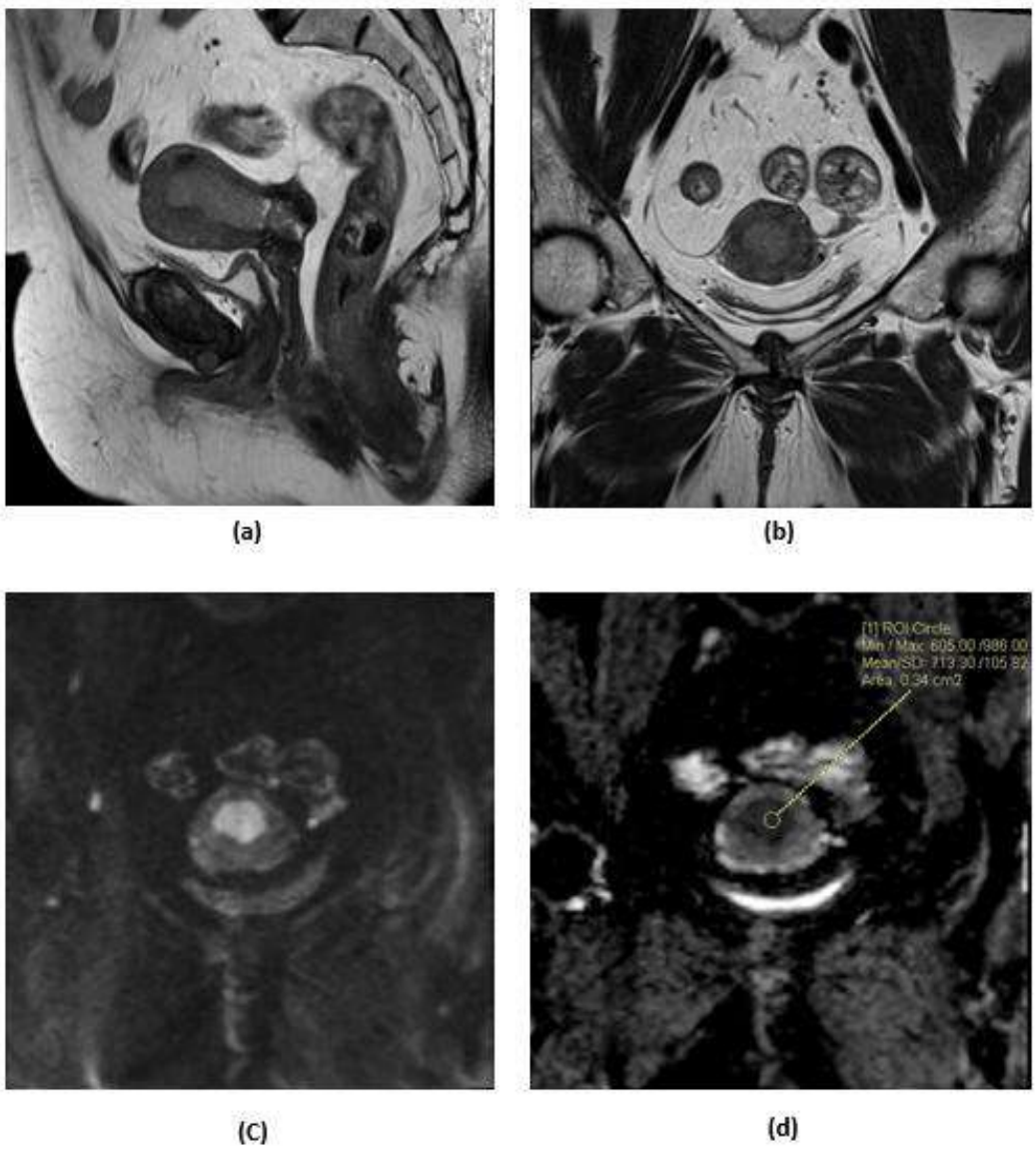


Figure 25: 66 year old patient, presented with post-menopausal vaginal bleeding.

(a and **b)** Sagittal and axial T2WI: show intermediate signal intensity endometrial lesion. **c)** Axial DWI show bright signal of the endometrial lesion. **(d)** Corresponding ADC map show dark signal of the endometrial lesion with mean ADC value of 0.71 x 10^{-3} mm^2/sec. Histopathologically, the lesion was proved as endometrial carcinoma.

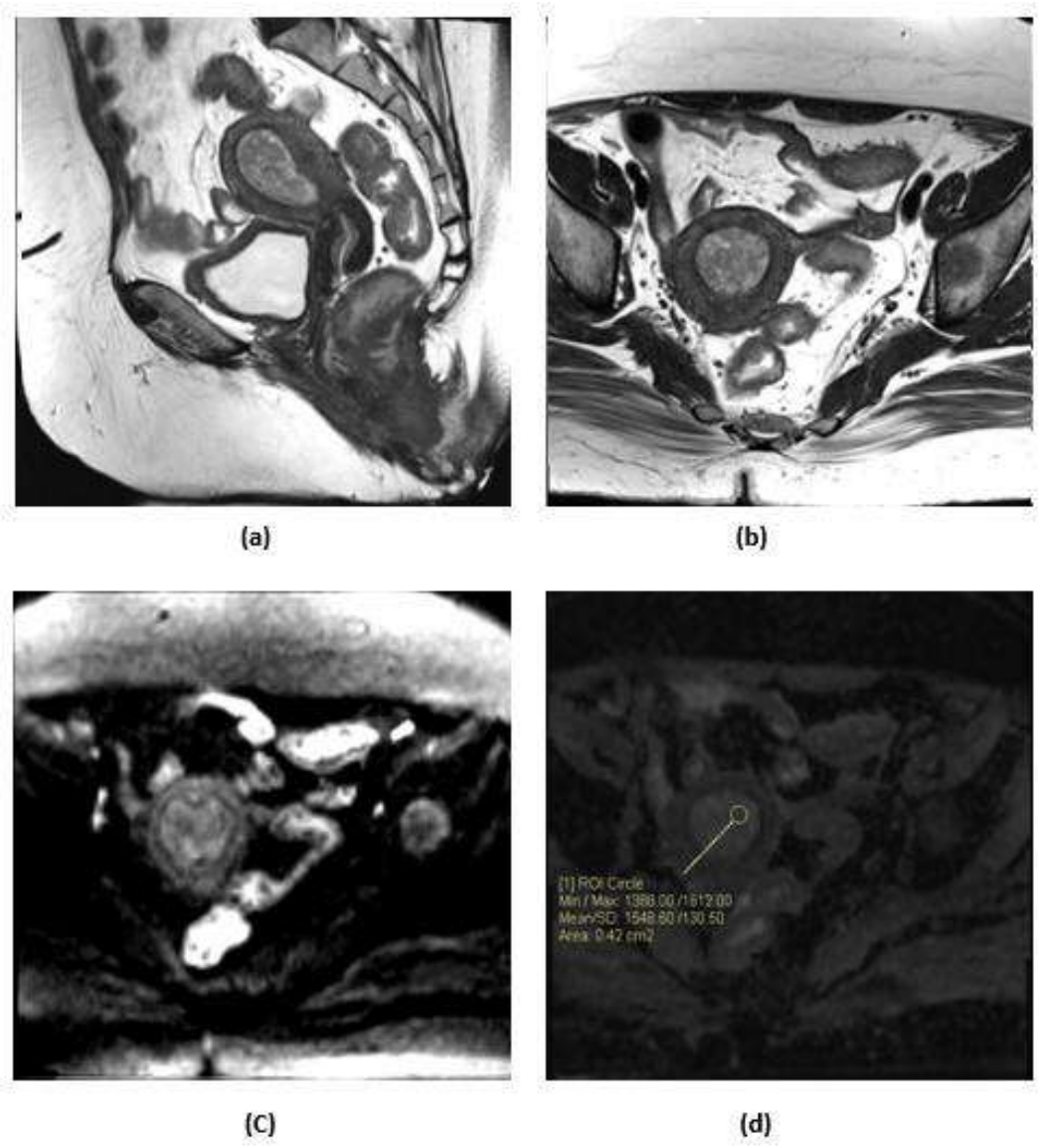


Figure 26: 63 year old patient, presented with post-menopausal bleeding.

(a and **b)** Sagittal and axial T2WI show heterogeneously hypointense endometrial lesion with small interspersed cystic areas. **(c)** Axial DWI show heterogeneously bright signal of the endometrial lesion. **(d)** Corresponding ADC map also show bright signal of the endometrial lesion with mean ADC value of1.55 x 10^{-3} mm^2/sec. Histopathologically, the endometrial lesion was proved as benign endometrial polyp.

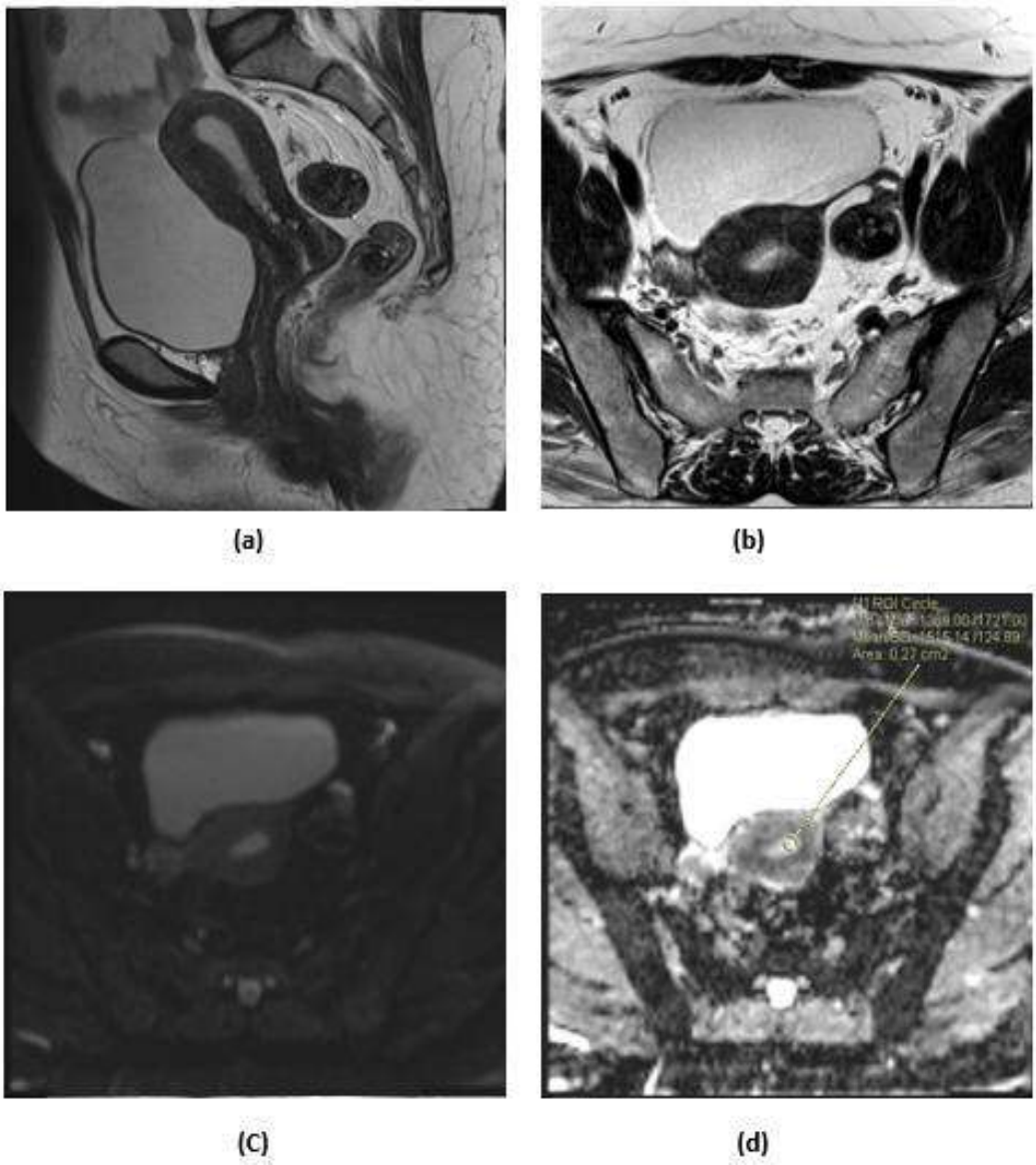


Figure 27: 50 year old post-menopausal patient presented with post-menopausal bleeding.

(a and **b)** Sagittal and axial T2WI show hyperintense endometrium which measured 10mm in thickness. **(c and d)** Axial DWI and corresponding ADC map both show bright signal of the endometrium with mean ADC value of1.51 x 10^{-3} mm^2/sec. Histopathologically, proved as endometrial hyperplasia.

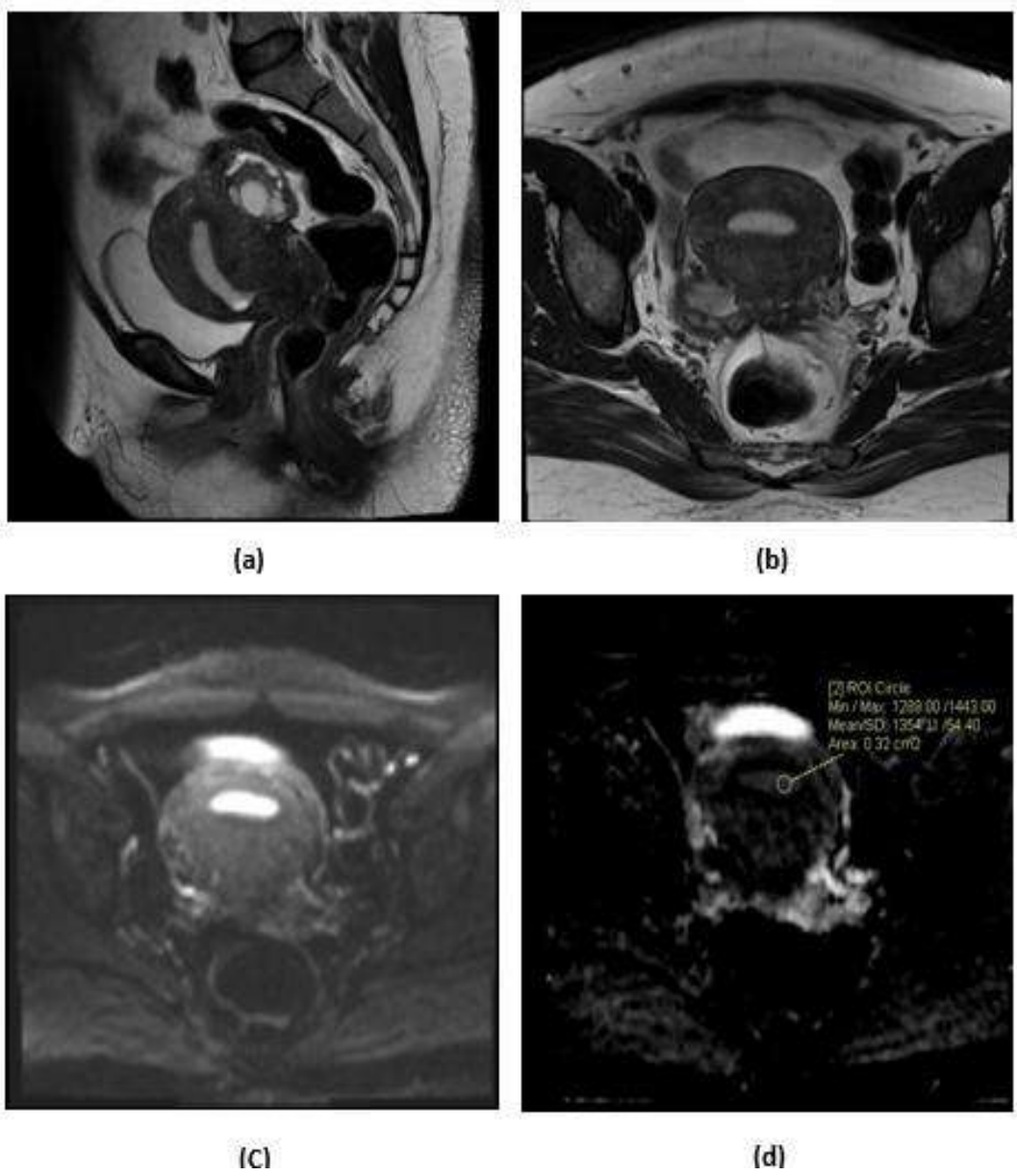


Figure 28: 41 year old pre-menopausal patient presented with lower abdominal pain.

(a and **b)** Sagittal and Axial oblique T2-WI show homogenously hyperintense endometrium. **(c and d)** Both Axial DWI and corresponding ADC mapshow bright signal of endometrium with mean ADC value of 1.35 X $10^{-3}mm^2/s$. Histopathologically, revealed proliferative endometrium and bilateral ovarian endometriosis.

DISCUSSION

Endometrial carcinoma is the most common malignant tumour of the female pelvis and its incidence is steadily rising because of prolonged life span and escalating levels of obesity[64-66].

Diffusion-weighted MRI is considered a good functional imaging tool in diagnosis of gynaecologic diseases and has a promising role in evaluating patients with suspected pelvic malignancies as well. Generally, owing to their high cellularity, malignant tumours show diffusion restriction with low apparent diffusion coefficient (ADC) value compared to the benign lesions as well as normal tissues[45,67-70].

DWI together with ADC measurement can be used for diagnostic purposes in conditions of difficult endometrial biopsy or curettage due to the presence of endometrial atrophy, adhesions, and the requirement of anaesthesia in aged patients.

40 patients with endometrial lesions were enrolled in our study with the age range of 26-82 years and mean age of 58 years. The most common affected age group was between 61 and 70 years. Concordantly, in a study done by Elsammak et al.[61] the most common age range of patients presenting with endometrial pathologies was 60-70 years.

In the current study, the role of diffusion weighted image in characterization of endometrial lesions was evaluated by determining their ADC values. We found that endometrial lesions displayed variable signal intensities on diffusion weighted images. However, on the basis of diffusion weighted images alone it was difficult to differentiate malignant endometrial lesions from benign endometrial lesions and normal endometrium. So, in current study role of diffusion weighted images along with quantitative ADC values was evaluated to differentiate malignant endometrial lesions from benign endometrial lesions and normal endometrium.

In series of studies by Masroor et al.[53], Malayeri et al.[71] and Dhanda et al.[72] it was opined that although DWI is helpful in

demonstrating endometrial malignant lesions, however, it is difficult to differentiate normal tissue from cancerous tissue based only on the increased signal intensity of endometrium.

In current study, endometrial malignant lesions (n=21) displayed bright signal on DWI and corresponding dark signal on ADC map with range of ADC values between 0.62 - 0.96 x 10^{-3} mm^2/sec and mean ADC value of 0.75 ± 0.09 x 10^{-3} mm^2/sec (at b-value of 800 s/mm^2).

Our result is similar to a study by Masroor et al.[53] who evaluated the role of diffusion and ADC in 52 cases of endometrial carcinoma. The mean ADC value for endometrial carcinoma was 0.730 ± 0.215 x 10^{-3} mm^2/sec.

The current study is also in agreement with Elsammak et al.[61] study who enrolled 18 patients of malignant endometrial lesions in their study and reported that mean ADC value of malignant endometrial lesion was 0.82 ± 0.23 x 10^{-3} mm^2 /sec (range: 0.58 – 1.09 x 10^{-3} mm^2 /sec).

Fujii et al.[41] retrospectively evaluated 13 patients with endometrial malignancies and found that mean ADC value of malignant endometrial lesions was 0.98 ± 0.19 x 10^{-3} mm^2 /sec.

In another study by Wang et al.[73] in 28 patients of endometrial cancer the mean ADC value was 0.88 ± 0.16 x 10^{-3} mm^2 /sec.

Shen et al.[51] evaluated ADC values (at b value of 1000 s/mm^2) of 24 endometrial malignant lesions and reported that the mean ADC value of malignant endometrial lesions was 0.864 ± 0.31 x 10^{-3} mm^2/sec.

The present study is concordant with Tamai et al.[50] who reported mean ADC value of 0.88 ± 0.16 x 10^{-3} mm^2/sec in malignant endometrial lesions while evaluating feasibility of diffusion-weighted (DW) MRI in endometrial cancer in 18 patients.

Bharwani et al.[55] used different b-values (0, 50, 100, 250, 500, 750 s/mm^2) to determine ADC values of 23 endometrial cancers and

documented mean ADC values of 0.97 ± 0.13 x 10^{-3} mm^2 /sec in endometrial cancers.

Takeuchi et al.[47] evaluated the role of diffusion weighted imaging in 45 patients with endometrial cancers recorded mean ADC value of 0.84 ± 0.19 x 10^{-3} mm^2/sec.

A study conducted by Rechichi et al.[56] reported mean ADC value of0.77 ± 0.12 x 10^{-3} mm^2/sec for endometrial carcinomas while enrolling 70 patients with endometrial carcinomas which is in agreement with current study.

Cavusoglu et al[59] study enrolled 52 patients, out of which 14 were pathologically proven endometrial cancers and reported mean ADC value of endometrial cancer was 0.88 ± 0.10 x 10^{-3} mm^2/sec.

In the current study, benign endometrial lesions (endometrial hyperplasia and polyps) displayed bright signal intensity on both DW image and corresponding ADC maps with range of ADC values between 1.01 - 1.95 x 10^{-3} mm^2/sec and mean ADC of 1.50 ± 0.26 x 10^{-3} mm^2/sec at b-value of 800 s/mm^2.

The current study is in agreement with study conducted by Bharwani et al.[55] on 19 benign endometrial lesions, in which the mean ADC value of benign endometrial lesions was 1.50 ± 0.14x 10^{-3} mm^2/sec (at b-value of 750 s/mm^2).

Elsammak et al.[61] also in their study on 24 benign endometrial lesions reported ADC value of 1.44 ± 0.15 x 10^{-3} mm^2/sec (range: 1.33 – 1.77 x 10^{-3} mm^2 /sec).

Current study is concordant with study of Takeuchi et al.[47] who included 22 patients with benign endometrial lesions (hyperplasia and polyps) in his study and recorded mean ADC value of 1.58 ± 0.36 x 10^{-3} mm^2/sec for benign endometrial lesions.

Shen et al.[51] who evaluated ADC values (at b-value of 1000 s/mm^2) of 7 endometrial benign lesions and reported that the mean ADC value of benign endometrial conditions (such as endometrial hyperplasia and endometrial polyps) was 1.27±0.22 x 10^{-3} mm^2/sec.

Cavusoglu et al.[59] evaluated 38 patients of benign endometrial lesions (27 were endometrial hyperplasia and 11 were polyps) and reported mean ADC value of 1.78 ± 0.27x 10^{-3} mm^2/sec.

In current study, the controls with normal endometrium showed bright signal on both diffusion weighted images and corresponding ADC maps with ADC values ranging between 1.17 - 1.88 x 10^{-3} mm^2/sec and mean ADC value of 1.41 ± 0.14 x 10^{-3} mm^2/sec at b-value of 800 s/mm^2.

The current study is in agreement with Wang et al.[73] study who studied 30 patients with normal endometrium and found that the mean ADC of normal endometrium 1.446 ± 0.246 x 10^{-3} mm^2/sec.

Tamai et al.[50] evaluated 12 cases with normal endometrium and reported mean ADC value of 1.53 ± 0.10 x 10^{-3} mm^2/sec.

Masroor et al.[53] included 40 controls with normal endometrium in his study and discovered mean ADC value of 1.26 ± 0.30 x10-3 mm^2/sec for normal endometrium.

Rechichi et al.[56] reported mean ADC value of 1.31 ± 0.11x 10^{-3} mm^2/sec for normal endometrium while evaluating 36 controls.

In current study, we found statistically significant difference between the mean ADC values of malignant lesions (0.75 ± 0.09 x 10^{-3} mm^2/sec) and benign lesions (1.50 ± 0.26 x 10^{-3} mm^2/sec) as well as between the mean ADC values of malignant masses (0.75 ± 0.09 x 10^{-3} mm^2/sec) and normal endometrium (14.10 ± 0.14 x10^{-3} mm^2/sec) with p value of 0.001.

We have found that measurement of ADC value has a potential capability to differentiate malignant endometrial lesions from benign endometrial lesions and normal endometrium as ADC value was much lower in malignant endometrial lesions as compared to benign endometrial lesions and normal endometrium.

In the current study, using 1.03 x 10^{-3} mm^2/sec as a cut off value for distinguishing malignant from benign endometrial lesions, we found 94.7% sensitivity, 100% specificity, 100% PPV, 95.4% NPV and accuracy of 97.5% with statistically significant p-value of 0.001.

This is in concordance with study done by Elsammak et al.[61] study who found statistically significant low mean ADC value for 18 endometrial carcinoma (0.82 ± 0.23 x 10^{-3} mm^2/sec) as compared to 24 benign lesions (1.44 ± 0.15 x 10^{-3} mm^2/sec). He considered 1.19 x 10^{-3} mm^2/sec as a cut-off value for distinguishing malignant from benign lesion his study had 88.9% sensitivity, 100% specificity, 100% PPV and 92% NPV with highly significant P value = 0.000.

The current study is in agreement with Fujii et al.[41] who reported statistically significant difference between ADC values of malignant (0.98 ± 0.19) and benign lesions (1.44 ± 0.34) (P<0.01). He defined malignant tumours as cases with an ADC value less than 1.15 × 10^{-3} mm^2/sec for obtaining the highest accuracy with sensitivity, specificity, and accuracy 84.6%, 100%, and 92%, respectively.

Current study is in agreement with Bharwani et al.[55] who reported low mean ADC values for endometrial carcinoma (n=23) which was 0.97 ± 0.31×10^{-3} mm^2/sec as compared to benign lesions (19) which was 1.50 ± 0.14 ×10^{-3} mm^2/s and using 1.28 ×10^{-3} mm^2/sec as cut-off ADC value achieved a sensitivity 87%, specificity 100%, positive predictive value 100% and negative predictive value 85.7% with statistically significant p-value (< 0.0001) for malignancy.

Takeuchi et al.[47] study reported mean ADC values of 45 malignant endometrial lesions was 0.84 x 10^{-3} mm^2/sec and 22 benign lesions was 1.58 ± 0.36 x 10^{-3} mm^2/sec with statistically significant difference between endometrial cancers and benign lesions (P < 0.01) when using ADC of 1.21 ± 0.36 x 10^{-3} mm^2/sec as cut off value with 96% sensitivity, 95% specificity, 98% PPV and 91% NPV for malignant lesions.

Masroor et al.[53] study on 52 patients with endometrial malignant lesions showed low mean ADC value (0.73 ± 0.21 x10^{-3} mm^2/sec)

as compared to 52 controls having normal endometrium (1.26 ± 0.305x10^{-3} mm^2/sec) with statistically significant p-value (0.001).

This study is in concordance with study done by Inada et al.[52] who enrolled 22 endometrial carcinomas and 31 normal endometrium, and revealed lower mean ADC values for endometrial carcinoma (0.97 ± 0.19 × 10^{-3} mm^2/sec) as compared to the normal endometrium (1.52 ± 0.20× 10^{-3} mm^2/sec).

Table 34: Comparing mean ADC values of malignant and benign endometrial lesions

Author, year	b-value (s/mm2)	Number of malignant lesions	Number of benign lesions	Mean (±SD) ADC value of malignant lesions (×10–3 mm2/s)	Mean (±SD) ADC value of benign lesions (×10–3 mm2/s)
Current study, 2022	5,04,00,800	21	18	0.75 (±0.09)	1.50 (±0.26)
Mansour, 2019 [63]	1000	17	21	0.86 (±0.15)	1.74 (±0.15)
Elsammak, 2017 [61]	0,800,1000	18	24	0.82 ± 0.23	1.44 ± 0.15
Bharwani, 2014 [55]	0,750	23	19	0.97 ± 0.31	1.50 ± 0.14
Takeuchi, 2009 [47]	0, 800	45	22	0.84 (±0.19)	1.58 (±0.36)
Shen, 2008 [51]	5,00,80,01,000	24	7	0.86 ± 0.31	1.27 ± 0.22
Fujii, 2008 [41]	0,1000	13	12	0.98 ± 0.19	1.44 ± 0.34

Table 35: Comparison of apparent diffusion coefficient (ADC) threshold values, sensitivity, specificity, PPV and NPV to differentiate malignant and benign endometrial lesions

Author, year	ADC threshold (×10–3 mm2 /s)	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Current study, 2022	1.03	94.7	100	100	95.5
Takeuchi, 2009 [47]	1.21	96	95	98	91
Bharwani, 2014 [55]	1.28	87	100	100	85.7
Elsammak,2017 [61]	1.19	88.9	100	100	92

PPV-Positive predictive value, NPV-Negative predictive value

In the current study the endometrial hyperplasia and endometrial polyps individually showed the mean ADC values of 1.49 ± 0.24 x 10^{-3} mm^2/sec and 1.51 ± 0.29 x 10^{-3} mm^2/sec respectively. No statistically significant difference among the mean ADC values of benign endometrial lesions i.e., hyperplasia and polyp were found. Current study is in agreement with Elsammak et al.[61] study who reported that there was no statistically significant difference in ADC values among benign endometrial lesions and measured mean ADC value of 1.43 ± 0.15 x 10^{-3} mm^2/sec for endometrial hyperplasia and 1.63 ± 0.021 x 10^{-3} mm^2/sec for endometrial polyps.

In the current study the normal endometrium and benign endometrial lesions showed the mean ADC values of 1.41 ± 0.14 x 10^{-3} mm^2/sec and 1.50 ± 0.26 x 10^{-3} mm^2/sec respectively. No statistically significant difference was found between the mean ADC values of normal endometrium and benign endometrial lesions.

The results of current study showed high sensitivity reassuring in differentiating malignant endometrial lesions from benign endometrial lesions. DWI with ADC values can be very helpful in elderly patients with impaired renal functions or in patients with allergy to contrast media.

LIMITATIONS

There were some shortcomings in the present study which included firstly the small sample size. Secondly, in our experience, there was a low incidence of endometrial hyperplasia. Therefore, further multicentric longitudinal research on larger scales is warranted to validate the findings of the current study.

SUMMARY AND CONCLUSION

1. The present study was conducted at the Department of Radiodiagnosis, Dayanand Medical College and Hospital, Ludhiana.
2. The study was conducted on 40 patients with abnormal endometrial thickening on MRI between the period of 01 March 2021 to 28 February 2022. These included 21 malignant endometrial lesions, 11 endometrial hyperplasia and 8 polyps which were proven histopathologically. 30 controls with normal endometrium were included in the study.
3. Magnetic resonance imaging was performed in all patients on SIEMENS MAGNETOM SKYRA 48 Channel 3 Tesla MRI using T1-weighted imaging, T2-weighted imaging and diffusion weighted imaging.
4. The age range of patients was from 26-82 years with maximum number of patients in post-menopausal age group.
5. The most common presenting symptom was post-menopausal bleeding seen in 62.5% patients.
6. Statistically significant difference between the mean ADC values of malignant endometrial lesions ($0.75 \pm 0.09 \times 10^{-3}$ mm^2/sec) and benign endometrial lesions ($1.50 \pm 0.26 \times 10^{-3}$ mm^2/sec) with p value of 0.001.
7. Using 1.03×10^{-3} mm^2/sec as a cut off value for distinguishing malignant from benign endometrial lesions, it showed 94.7% sensitivity, 100% specificity, 100% PPV, 95.4% NPV and accuracy of 97.5% with statistically significant p-value of 0.001.
8. There was statistically significant difference between the mean ADC values of malignant lesions ($0.75 \pm 0.09 \times 10^{-3}$ mm^2/sec) and normal endometrium ($1.41 \pm 0.14 \times 10^{-3}$ mm^2/sec) with p value of 0.001.
9. Mean ADC values of endometrial hyperplasia and endometrial polyps measured $1.49 \pm 0.24 \times 10^{-3}$ mm^2/sec and $1.51 \pm 0.29 \times 10^{-3}$ mm^2/sec respectively.

10. No statistically significant difference in mean ADC values was found among benign endometrial lesions i.e., endometrial hyperplasia and polyps in the current study.
11. No statistically significant difference was found between mean ADC values of normal endometrium ($1.41 \pm 0.14 \times 10^{-3}$ mm^2/sec) and benign endometrial lesions ($1.50 \pm 0.26 \times 10^{-3}$ mm^2/sec) in the current study.

CONCLUSION

1. Diffusion weighted magnetic resonance imaging is a sensitive tool in detection of endometrial cancer.
2. The ADC values in malignant lesions are significantly lower than the benign endometrial lesions and normal endometrium.
3. Using DWI with ADC values, malignant lesions can be differentiated from benign endometrial lesions and normal endometrium.
4. In patients with renal dysfunction or allergic to gadolinium based contrast DWI with ADC values can be helpful in the detection of endometrial cancer in non enhanced MRI.
5. Benign endometrial lesions like polyps and hyperplasia cannot be differentiated from each other only on the basis of ADC values.
6. Using only ADC values, normal endometrium and benign endometrial lesions cannot be differentiated from each other.

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PROFORMA

S. No

Date:

Name: Age/Sex:

MRD No.: Contact no.:

Address:

Co-Morbidity: 1) Diabetes 2) Hypertension 3) CAD 4) Others

History of : Carcinoma in Family Yes No

Hormone Replacement Therapy Yes No

LMP:

Menstrual Status: 1) Reproductive

2) Postmenopausal

Presenting Complaints:

1) Abnormal vaginal bleeding

2) Post-menopausal bleeding

3) Lower abdominal pain

4) Others

5) Incidentally detected (mode of detection)

Signature of Candidate

Signature of Supervisor

EXAMINATION

1)General Physical Examination:

2) Pelvic examination:

3) Lab Investigations:

- Hemogram

- RFTs

- Ultrasound Findings:

Signature of Candidate **Signature of Supervisor**

MRI FINDINGS

Endometrial Thickness:

DIFFUSION WEIGHTED IMAGES (DWI):

Signal intensity	Bright/ Dark
ADC value	

T1W IMAGING:

T2W IMAGING:

Histopathology (wherever done):

FINAL DIAGNOSIS:

Signature of Candidate **Signature of Supervisor**

S.No.	NAME	MRD	group	AGE (YEARS)	Menopausal Status	Clinical complaints	Diabetes
1	S	1259174	Malignant endometrial lesion	56	Post-menopausal	Post-menopausal bleeding	No
2	P	1252698	Malignant endometrial lesion	50	Pre-menopausal	Abnormal vaginal bleeding	No
3	PK	1245214	Malignant endometrial lesion	49	Pre-menopausal	Abnormal vaginal bleeding	No
4	PD	1238863	Malignant endometrial lesion	35	Pre-menopausal	Abnormal vaginal bleeding	No
5	KD	297340	Malignant endometrial lesion	66	Post-menopausal	Post-menopausal bleeding	No
6	BK	1151819	Malignant endometrial lesion	65	Post-menopausal	Post-menopausal bleeding	Yes
7	KK	1127772	Malignant endometrial lesion	64	Post-menopausal	Post-menopausal bleeding	No
8	RR	1118103	Malignant endometrial lesion	57	Post-menopausal	Post-menopausal bleeding	Yes
9	NB	1272213	Malignant endometrial lesion	60	Post-menopausal	Post-menopausal bleeding	No
10	RM	592834	Malignant endometrial lesion	45	Pre-menopausal	Abnormal vaginal bleeding	No
11	SK	1058466	Malignant endometrial lesion	46	Pre-menopausal	Abnormal vaginal bleeding	Yes
12	MB	1157983	Malignant endometrial lesion	69	Post-menopausal	Post-menopausal bleeding	No
13	BK	1307678	Malignant endometrial lesion	42	Pre-menopausal	Post-menopausal bleeding	No
14	AG	1390023	Malignant endometrial lesion	63	Post-menopausal	Post-menopausal bleeding	No
15	RK	1393913	Malignant endometrial lesion	72	Post-menopausal	Post-menopausal bleeding	No
16	KK	1173567	Malignant endometrial lesion	58	Post-menopausal	Post-menopausal bleeding	Yes
17	SD	1386057	Malignant endometrial lesion	82	Post-menopausal	Post-menopausal bleeding	Yes
18	AG	1410562	Malignant endometrial lesion	68	Post-menopausal	Post-menopausal bleeding	No
19	KR	1430701	Malignant endometrial lesion	65	Post-menopausal	Post-menopausal bleeding	Yes
20	S	1436550	Malignant endometrial lesion	74	Post-menopausal	Post-menopausal bleeding	Yes
21	KK	1290247	Malignant endometrial lesion	65	Post-menopausal	Post-menopausal bleeding	No
22	NJ	346786	Polyps	63	Post-menopausal	Post-menopausal bleeding	No
23	SB	655691	Polyps	64	Post-menopausal	Post-menopausal bleeding	No
24	SD	1019752	Polyps	65	Post-menopausal	Post-menopausal bleeding	No
25	A	1152391	Polyps	73	Post-menopausal	Post-menopausal bleeding	No
26	AK	1236157	Polyps	50	Pre-menopausal	Abnormal vaginal bleeding	No
27	VD	1206950	Polyps	64	Post-menopausal	Post-menopausal bleeding	Yes
28	ST	1187506	Polyps	26	Pre-menopausal	Abnormal vaginal bleeding	No
29	KK	1335694	Polyps	50	Pre-menopausal	Abnormal vaginal bleeding	No
30	PK	1434307	Polyps	62	Post-menopausal	Post-menopausal bleeding	No
31	A	1280093	Polyps	48	Pre-menopausal	Abnormal vaginal bleeding	Yes
32	S	1423624	Polyps	50	Pre-menopausal	Abnormal vaginal bleeding	No
33	JK	1399200	Endometrial hyperplasia	60	Post-menopausal	Lower abdominal pain	No
34	SK	1263705	Endometrial hyperplasia	35	Pre-menopausal	Lower abdominal pain	No
35	MJ	1393149	Endometrial hyperplasia	57	Post-menopausal	incidentally detected	Yes
36	RK	1152360	Endometrial hyperplasia	70	Post-menopausal	incidentally detected	No
37	RP	821102	Endometrial hyperplasia	67	Post-menopausal	Post-menopausal bleeding	No
38	MK	941491	Endometrial hyperplasia	50	Post-menopausal	Post-menopausal bleeding	No
39	S	929064	Endometrial hyperplasia	70	Post-menopausal	Post-menopausal bleeding	Yes
40	B	207291	Endometrial hyperplasia	51	Post-menopausal	Lower abdominal pain	No
41	SK	5947	Normal endometrium	53	Post-menopausal	Post-menopausal bleeding	Yes

S.No.	NAME	Co-morbidities		Endometrial Thickness (mm)	Signal on T2	Signal on T1	DWI signal
		Hypertension	Others				
1	S	Yes	No	15	Intermediate	Intermediate	Bright
2	P	No	No	16	Intermediate	Hypointense	Bright
3	PK	No	Hypothyroid	28	Intermediate	Intermediate	Bright
4	PD	No	No	17	Intermediate	Hypointense	Bright
5	KD	No	Migraine	68	Intermediate	Intermediate	Bright
6	BK	No	No	38	Intermediate	Intermediate	Bright
7	KK	Yes	No	38	Intermediate	Intermediate	Bright
8	RR	No	No	16	Intermediate	Hypointense	Bright
9	NB	No	No	26	Intermediate	Intermediate	Bright
10	RM	No	Bronchial asthma	26	Intermediate	Intermediate	Mixed areas of bright and dark signal
11	SK	No	No	33	Intermediate	Hypointense	Bright
12	MB	No	No	40	Intermediate	Hypointense	Bright
13	BK	No	No	10	Intermediate	Intermediate	Bright
14	AG	No	No	20	Intermediate	Hypointense	Bright
15	RK	Yes	No	80	Intermediate	Hypointense	Mixed areas of bright and dark signal
16	KK	No	Hypothyroid	8.5	Intermediate	Intermediate	Bright
17	SD	No	No	33	Intermediate	Intermediate	Bright
18	AG	No	No	14	Intermediate	Intermediate	Bright
19	KR	Yes	Bronchial asthma	13.3	Intermediate	Hypointense	Bright
20	S	No	No	28	Intermediate	Hypointense	Bright
21	KK	Yes	No	16	Intermediate	Intermediate	Bright
22	NJ	No	No	23	Heterogenously hypointense and cystic	Hypointense	Dark
23	SB	No	Hypothyroid	9	Heterogenously hypointense and cystic	Hypointense	Dark
24	SD	No	No	13	Heterogenously hypointense and cystic	Hypointense	Dark
25	A	Yes	No	7.7	Intermediate	Hypointense	Mixed areas of bright and dark signal
26	AK	No	No	17	Intermediate	Hypointense	Dark
27	VD	No	No	10	Intermediate	Hypointense	Bright
28	ST	No	No	15	Intermediate	Intermediate	Bright
29	KK	No	No	8	Intermediate	Hypointense	Bright
30	PK	No	No	8.1	Intermediate	Hypointense	Bright
31	A	No	No	16	Intermediate	Hypointense	Bright
32	S	Yes	Migraine	14.5	Intermediate	Intermediate	Bright
33	JK	No	No	14	Homogenously hyperintense	Hypointense	Bright
34	SK	No	No	19	Homogenously hyperintense	Hypointense	Bright
35	MJ	No	No	14	Intermediate	Hypointense	Bright
36	RK	No	No	7	Homogenously hyperintense	Hypointense	Bright
37	RP	No	No	8	Homogenously hyperintense	Hypointense	Bright
38	MK	No	No	10	Intermediate	Hypointense	Bright
39	S	No	No	7	Homogenously hyperintense	Hypointense	Bright
40	B	No	No	16	Homogenously hyperintense	Hypointense	Bright
41	SK	No	No	4	Homogenously hyperintense	Hypointense	Bright

S.No.	NAME	ADC	ADC value ($X^{10-3}mm^2/sec$)	HISTOPATHOLOGY
1	S	Dark and heterogenous	0.88	Yes
2	P	Dark	0.79	Yes
3	PK	Dark	0.68	Yes
4	PD	Dark	0.66	Yes
5	KD	Dark	0.72	Yes
6	BK	Dark	0.72	Yes
7	KK	Dark	0.86	Yes
8	RR	Dark	0.82	Yes
9	NB	Dark	0.69	Yes
10	RM	Dark and heterogenous	0.85	Yes
11	SK	Dark	0.83	Yes
12	MB	Dark	0.63	Yes
13	BK	Dark	0.69	Yes
14	AG	Dark	0.76	Yes
15	RK	Dark and heterogenous	0.95	Yes
16	KK	Dark	0.85	Yes
17	SD	Dark	0.81	Yes
18	AG	Dark	0.62	Yes
19	KR	Dark	0.69	Yes
20	S	Dark	0.65	Yes
21	KK	Dark	0.68	Yes
22	NJ	Bright	1.60	Yes
23	SB	Bright	1.65	Yes
24	SD	Bright	1.90	Yes
25	A	Dark	1.05	Yes
26	AK	Bright	1.57	Yes
27	VD	Bright	1.54	Yes
28	ST	Bright	1.59	Yes
29	KK	Bright	1.21	Yes
30	PK	Bright	1.62	Yes
31	A	Dark	1.01	Yes
32	S	Bright	1.83	Yes
33	JK	Bright	1.50	Yes
34	SK	Bright	1.47	Yes
35	MJ	Bright	1.25	Yes
36	RK	Bright	1.95	Yes
37	RP	Bright	1.72	Yes
38	MK	Bright	1.43	Yes
39	S	Bright	1.26	Yes
40	B	Bright	1.37	Yes
41	SK	Bright	1.31	No

S.No.	NAME	MRD	group	AGE (YEARS)	Menopausal Status	Clinical complaints	Diabetes
42	SK	793698	Normal endometrium	52	Post-menopausal	Lower abdominal pain	No
43	DK	1189238	Normal endometrium	52	Post-menopausal	Post-menopausal bleeding	No
44	PK	908060	Normal endometrium	55	Post-menopausal	Post-menopausal bleeding	No
45	B	1126361	Normal endometrium	45	Pre-menopausal	Lower abdominal pain	Yes
46	M	840836	Normal endometrium	39	Pre-menopausal	Lower abdominal pain	No
47	SK	1137434	Normal endometrium	41	Pre-menopausal	Lower abdominal pain	No
48	RG	1126551	Normal endometrium	37	Pre-menopausal	Lower abdominal pain	No
49	SS	140392	Normal endometrium	34	Pre-menopausal	Lower abdominal pain	No
50	HK	347352	Normal endometrium	27	Pre-menopausal	Lower abdominal pain	No
51	PK	1220027	Normal endometrium	49	Pre-menopausal	Lower abdominal pain	Yes
52	M	1018090	Normal endometrium	28	Pre-menopausal	Abnormal vaginal bleeding	No
53	AK	1196536	Normal endometrium	30	Pre-menopausal	Lower abdominal pain	No
54	PK	1196567	Normal endometrium	35	Pre-menopausal	Lower abdominal pain	No
55	AK	797193	Normal endometrium	26	Pre-menopausal	Lower abdominal pain	No
56	PK	417865	Normal endometrium	29	Pre-menopausal	Lower abdominal pain	No
57	MG	1130153	Normal endometrium	42	Pre-menopausal	Facial growth	No
58	M	1180399	Normal endometrium	40	Pre-menopausal	Lower abdominal pain	No
59	B	1123487	Normal endometrium	43	Pre-menopausal	Abnormal vaginal bleeding	No
60	RS	1274968	Normal endometrium	35	Pre-menopausal	Lower abdominal pain	No
61	RJ	346895	Normal endometrium	47	Pre-menopausal	Lower abdominal pain	No
62	KK	1246286	Normal endometrium	37	Pre-menopausal	Lower abdominal pain	No
63	HS	1197810	Normal endometrium	41	Pre-menopausal	Lower abdominal pain	No
64	SJ	803463	Normal endometrium	41	Pre-menopausal	Abnormal vaginal bleeding	No
65	DS	1139738	Normal endometrium	41	Pre-menopausal	Lower abdominal pain	Yes
66	NK	1130248	Normal endometrium	44	Pre-menopausal	Lower abdominal pain	No
67	DJ	1270078	Normal endometrium	36	Pre-menopausal	Lower abdominal pain	No
68	RJ	721872	Normal endometrium	41	Pre-menopausal	Lower abdominal pain	No
69	BK	1071341	Normal endometrium	49	Pre-menopausal	Abnormal vaginal bleeding	No
70	RS	1126361	Normal endometrium	45	Pre-menopausal	Lower abdominal pain	No

S.No.	NAME	Co-morbidities		Endometrial Thickness (mm)	Signal on T2	Signal on T1	DWI signal
		Hypertension	Others				
42	SK	No	No	4.4	Homogenously hyperintense	Hypointense	Bright
43	DK	Yes	Migraine	4.8	Homogenously hyperintense	Hypointense	Bright
44	PK	No	No	5	Homogenously hyperintense	Hypointense	Bright
45	B	No	rheumatoid arthritis	8	Homogenously hyperintense	Hypointense	Bright
46	M	No	No	6	Homogenously hyperintense	Hypointense	Bright
47	SK	Yes	No	6	Homogenously hyperintense	Hypointense	Bright
48	RG	No	Bronchial asthma	9	Homogenously hyperintense	Hypointense	Bright
49	SS	No	No	10	Homogenously hyperintense	Hypointense	Bright
50	HK	No	No	7	Homogenously hyperintense	Hypointense	Bright
51	PK	Yes	No	8.1	Homogenously hyperintense	Hypointense	Bright
52	M	No	No	7	Homogenously hyperintense	Hypointense	Bright
53	AK	No	No	7	Homogenously hyperintense	Hypointense	Bright
54	PK	No	No	6.5	Homogenously hyperintense	Hypointense	Bright
55	AK	No	Migraine	8	Homogenously hyperintense	Hypointense	Bright
56	PK	No	No	7	Homogenously hyperintense	Hypointense	Bright
57	MG	No	No	7	Homogenously hyperintense	Hypointense	Bright
58	M	Yes	No	8	Homogenously hyperintense	Hypointense	Bright
59	B	No	No	8	Homogenously hyperintense	Hypointense	Bright
60	RS	No	Migraine	6.4	Homogenously hyperintense	Hypointense	Bright
61	RJ	Yes	No	5	Homogenously hyperintense	Hypointense	Bright
62	KK	No	No	12.3	Homogenously hyperintense	Hypointense	Bright
63	HS	No	No	4.8	Homogenously hyperintense	Hypointense	Bright
64	SJ	No	No	8	Homogenously hyperintense	Hypointense	Bright
65	DS	No	No	5.2	Homogenously hyperintense	Hypointense	Bright
66	NK	Yes	No	9	Homogenously hyperintense	Hypointense	Bright
67	DJ	No	Hypothyroid	14	Homogenously hyperintense	Hypointense	Bright
68	RJ	No	No	10.5	Homogenously hyperintense	Hypointense	Bright
69	BK	Yes	No	10	Homogenously hyperintense	Hypointense	Bright
70	RS	No	No	9.4	Homogenously hyperintense	Hypointense	Bright

S.No.	NAME	ADC	ADC value ($X^{10-3}mm^2/sec$)	HISTOPATHOLOGY
42	SK	Bright	1.36	No
43	DK	Bright	1.24	No
44	PK	Bright	1.41	No
45	B	Bright	1.36	Yes
46	M	Bright	1.25	No
47	SK	Bright	1.52	No
48	RG	Bright	1.18	No
49	SS	Bright	1.49	No
50	HK	Bright	1.45	No
51	PK	Bright	1.45	No
52	M	Bright	1.32	No
53	AK	Bright	1.41	No
54	PK	Bright	1.66	No
55	AK	Bright	1.28	No
56	PK	Bright	1.46	No
57	MG	Bright	1.52	Yes
58	M	Bright	1.36	Yes
59	B	Bright	1.36	Yes
60	RS	Bright	1.17	Yes
61	RJ	Bright	1.44	Yes
62	KK	Bright	1.50	Yes
63	HS	Bright	1.34	Yes
64	SJ	Bright	1.89	Yes
65	DS	Bright	1.29	Yes
66	NK	Bright	1.58	Yes
67	DJ	Bright	1.51	Yes
68	RJ	Bright	1.34	Yes
69	BK	Bright	1.38	No
70	RS	Bright	1.37	Yes

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Date 6/1/22

The Principal,
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.10.2021 has approved the plan of thesis of **Navdeep Singh**, a student of your college for **MD Radio-diagnosis** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

Role of mr diffusion weighted images(dwi) with apparent diffusion coefficient(adc) values in normaland pathological endometrium.

Supervisor

Dr. Archana Ahluwalia
Prof.,
Dept. of Radio-diagnosis,
DMCH, Ludhiana.

Co-Supervisor

Dr. Ashima Taneja
Prof. & Head,
Dept. of Obst. & Gynae.,
DMCH, Ludhiana.

Dr. Ritu Dhawan Galhotra
Prof.,
Dept. of Radio-diagnosis,
DMCH, Ludhiana.

The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

115. If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.

116. The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.

ROLE OF MR DIFFUSION WEIGHTED IMAGES (DWI) WITH APPARENT DIFFUSION COEFFICIENT (ADC) VALUES IN NORMAL AND PATHOLOGICAL ENDOMETRIUM

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED IN

PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MD

IN

RADIODIAGNOSIS

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

MARCH, 2021

DR. NAVDEEP SINGH

DEPARTMENT OF RADIODIAGNOSIS
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	Role of MR diffusion weighted images(DWI) with apparent diffusion coefficient(ADC) values in normal and pathological endometrium
For the degree of	MD (Radiodiagnosis)
Name of the candidate	Dr. Navdeep Singh
Supervisor	Dr. Archana Ahluwalia, Professor, Department of Radiodiagnosis, DMCH, Ludhiana
Co-supervisor(s)	Dr. Ashima Taneja, Professor & Head, Department of Obstetrics & Gynaecology, DMCH, Ludhiana Dr. Ritu Dhawan Galhotra, Professor, Department of Radiodiagnosis, DMCH, Ludhiana
Institution	Dayanand Medical College and Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

INTRODUCTION: Most endometrial pathologies show overlap in terms of imaging features with normal menstrual endometrial phases. There is a wide variation of ADC values of normal endometrium in reproductive age and postmenopausal women. The ADC values for endometrium are lower in the menstrual phase in comparison to the proliferative and the secretory phase. DWI with ADC values can be helpful in differentiation of benign from malignant endometrial lesions. Dense packed tissues with high cellularity such as cancers have a relatively little extracellular space leads to restricted water motion and hence shows lower ADC values as compared to the benign lesions as well as normal tissue.

AIM OF STUDY: To assess the role of MR DWI with ADC values in characterisation of endometrium into normal and pathological(benign and malignant) endometrium, and to correlate with histopathological examination wherever possible.

METHOD OF COLLECTION OF DATA: A prospective study will be done on all female patients referred for pelvic MRI to the Department of Radio-diagnosis, Dayanand Medical College and Hospital, Ludhiana over a period of 1 year. INCLUSION CRITERIA: All female patients undergoing pelvic MRI will be included in this study.

EXCLUSION CRITERIA: Patients in which ADC measurement is not possible due to thin endometrium or any technical factors, pregnant females and anyone unwilling to participate in the study.

CLINICAL SIGNIFICANCE: The most frequent gynecologic malignancy is endometrial cancer which should be discriminated from benign polyps and hyperplasia of the endometrium. The ADC value of benign endometrial lesion is significantly higher than malignant endometrial lesions. Therefore DWI with ADC values are useful in differentiating benign endometrial lesions from malignant endometrial lesions. A wide variation of ADC values of normal endometrial is detected during different periods of the menstrual cycle. Standard reference of ADC values of normal endometrium is helpful, serving as a baseline while interpreting endometrium pathologies.

Keywords: DWI, ADC, Menstural cycle, Endometrial carcinoma, Endometrium

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"ROLE OF MR DIFFUSION WEIGHTED IMAGES(DWI) WITH APPARENT DIFFUSION COEFFICIENT(ADC) VALUES IN NORMAL AND PATHOLOGICAL ENDOMETRIUM"** exist in the Department of Radiodiagnosis, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate herself under our supervision and guidance.

Supervisor

Dr. Archana Ahluwalia
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Place : DMCH, Ludhiana.

Date : 17/3/21

APPROVAL PROFORMA
BY RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr. Navdeep Sinhgh
Department	Radiodiagnosis
Topic of Thesis	Role of MR diffusion weighted images(DWI) with apparent diffusion coefficient(ADC) values in normal and pathological endometrium
Likely date of appearing in PG examination	May 2023
Date of enrollment	25 June 2020
Name of Head of Department	Dr. Kavita Saggar
1) **Supervisor** 2) **Co-Supervisor(s)**	Dr. Archana Ahluwalia Dr. Ashima Taneja Dr. Ritu Dhawan Galhotra
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
Dr. Harpreet Kaur (Professor & Head, Pathology)	Mr. R K Sharma (Legal Expert)
Dr. Jaspal Singh (Professor & Head, Surgery)	Dr. Ramit Mahajan (Associate Professor, Gastroenterology)
Dr. Dinesh Gupta (Professor & Head, Medicine)	Dr. Anu Sharma (Professor, Anatomy)
Dr. Sandeep Kaushal (Dean Academics & Professor & Head, Pharmacology)	Dr. Sandeep Kaushal (Dean Academics & Professor & Head, Pharmacology)
Dr. Gurpreet S Wander (Vice Principal)	Dr. Gurpreet S Wander (Vice Principal & Professor & Head, Cardiology)
	Dr. Gagandeep Singh (Secretary, Ethics Committee Professor & Head, Neurology)

Approved: Yes / No

Dr. Sandeep Puri
Chairperson
Research Committee

Approved: Yes / No

Prof. Arvind Malhotra
Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	Navdeep Singh H.No.19 W.No.10, Master Colony, Gurdaspur, Punjab-143521
2	NAME OF THE INSTITUTE	Dayanand Medical College and Hospital, Ludhiana
3	COURSE OF STUDY AND SUBJECT	M.D. Radiodiagnosis
4	DATE OF ADMISSION OF COURSE	25th June 2020
5	TITLE OF THE TOPIC	ROLE OF MR DIFFUSION WEIGHTED IMAGES(DWI) WITH APPARENT DIFFUSION COEFFICIENT(ADC) VALUES IN NORMAL AND PATHOLOGICA ENDOMETRIUM

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Diffusion weighted imaging (DWI) is a magnetic resonance imaging (MRI) sequence structured on the basis of diffusion (Brownian motion) of water molecules in the extracellular space and is being increasingly used to evaluate the female pelvis. The quantitative parameter acquired from DWI sequence is the apparent diffusion coefficient (ADC) value. The basic factors affecting the ADC values are tissue structures, interactions between the molecules and cellular density. Thus, ADC is altered by many physiological and pathological conditions of the body.[1]

DWI is acquired by the measurement of signal loss after a series of two motion-providing gradient (MPG) pulses with the addition of a 180° refocusing radio frequency pulse to both sides for enhancing the variations of molecular diffusion between tissues. The density of MPG pulses is shown by the b-value, a paramount criterion affecting the signal intensity of the DWI[2]. An appropriate b value is necessary for the female pelvic MRI.

On conventional MRI, the endometrial zone reflects high signal on T2-weighted sequences and low signal intensity on T1-weighted sequences[3].

Endometrial carcinoma is considered the most common female genital malignancy and the fourth most common type of female cancer [4].

On MR, endometrial carcinoma is usually diagnosed with a focally or diffusely thickened endometrium more than 10 mm in premenopausal patients and more than 4 mm in postmenopausal patients on sagittal T2-weighted images, and the signal intensity is low or intermediate relative to the that of normal endometrium.[5]

Normal endometrium thickness varies regularly in the course of the menstrual cycle; it becomes thickest (7-16 mm) during the secretory phase, which is partially overlapped with that of the diagnostic criteria of endometrial carcinoma[6]; secondarily, on the basis of morphologic features on T2-weighted MR images, endometrial carcinoma can not

be differentiated from endometrial polyp and hyperplasia.[7]

DW-MRI is a functional imaging technique that does not require the exogenous contrast medium administration required [8]. When DWI with ADC values is combined with T2 weighted MRI, it becomes a good diagnostic tool and provides more information for the differentiation and extension of benign and malignant lesions.[9-10]

Generally, dense packed tissues with high cellularity such as cancers have a relatively little extracellular space thus leads to restricted water motion and hence having lower ADC values compared to the benign lesions as well as normal tissues.[11-13]

The mean ADC values of malignant lesions detected in endometrial cavity and benign lesions have been reported to range between 0.84 and 0.98 × 10−3 s/mm2; 1.27 and 1.58 × 10−3 s/mm2, respectively.[7,14-17]

The ADC values of the endometrial zones are different in the three phases of the cycle (menstrual phase: 1.25± 0.27; proliferative phase: 1.39 ± 0.20; secretory phase: 1.50 ± 0.18 respectively).[18]

The endometrium is thin during menopause, endometrial biopsy samples are often scanty, depicting sparse remnants of narrow endometrial glands lined by a low epithelium with small inactive nuclei and supported by a dense fibrous stroma. This accounts for the lower ADC values in normal postmenopausal endometrium, when compared to the secretory phase of the menstrual cycle. On the other hand,during the secretory phase the functional layer of the endometrium thickens, with the uterine glands becoming larger and wavy and the arteries more prominent [19-21]. The increase of the interstitial fluid in the basal layer during this phase and the lower number of cells may represent other possible explanation for the higher ADC of the endometrium during the secretory phase.

A wide variation of ADC of normal endometrium is found between postmenopausal and reproductive age women. A standard reference of ADC of normal endometrium is helpful, serving as a baseline when interpreting endometrium pathologies.

6.2 REVIEW OF LITERATURE

Tamai et al [2007] evaluated 18 females with surgically proven endometrial cancer and 12 females with pathologically confirmed normal endometrium in cervical cancer patients. All endometrial cancer and the normal endometrium appeared hyperintense on DW images. The mean ADC value (10(-3) mm(2)/second) of endometrial cancer was 0.88 +/- 0.16, which was significantly lower (P < 0.01) than that of normal endometrium (1.53 +/- 0.10). The mean ADC value for each histologic grade was 0.93 +/- 0.16 (G1), 0.92 +/- 0.13 (G2), and 0.73 +/- 0.09 (G3).[14]

Fujii et al [2008] retrospectively evaluated 25 uterine endometrial cavity lesions in 25 female patients: endometrial carcinoma (n=11), carcinosarcoma (n=2), submucosal leiomyoma (n=8), and endometrial polyp (n=4). Diffusion weighted images were performed at 1.5 T with b factors of 0–1,000/mm2 . The region of interest was defined within the tumor on T2-weighted EPI image and then manually copied to an ADC map. Thereby, the ADC value was obtained. They compared ADC values between malignant and benign lesions using Student's t-test. The mean and standard deviation of ADC values (×10−3 mm2 /s) were as follows: endometrial carcinoma, 0.98±0.21; carcinosarcoma, 0.97±0.02; submucosal leiomyoma, 1.37±0.28; and endometrial polyp, 1.58±0.45. The ADC values differed significantly between malignant (0.98±0.19) and benign lesions (1.44±0.34) (P<0.01).They defined malignant tumors as cases with an ADC value less than 1.15×10−3 mm2 /s for obtaining the highest accuracy. Sensitivity, specificity, and accuracy were 84.6%, 100%, and 92%, respectively. ADC measurement can provide useful information in differentiating malignant from benign uterine endometrial cavity lesions.[15]

Inada et al [2009] evaluated 19 of 23 patients, endometrial cancers were detected only on T2-weighted images. In the remaining 4 patients, of whom two had coexisting leiomyoma, no cancer was detected on T2-weighted images. This corresponds to an 83% detection sensitivity for the carcinomas. When DW images and fused DW images/T2-weighted images were used in addition to the T2-

weighted images, cancers were identified in 3 of the remaining 4 patients in addition to the 19 patients (overall detection sensitivity of 96%). The mean ADC value of endometrial cancer (n=22) was (0.97+/-0.19)x10(-3)mm(2)/s, which was significantly lower than those of the normal endometrium, myometrium, leiomyoma and adenomyosis ($p<0.05$).[4]

Takeuchi et al [2009] evaluated Sixty-seven endometrial lesions including 45 cancers and 22 benign lesions (hyperplasia and polyps) by DWI with apparent diffusion coefficient (ADC) measurement. The staging accuracies of DWI and gadolinium enhanced T1-weighted images in the assessment of myometrial invasion were evaluated in 33 patients with endometrial cancer. The ADC values (x10(-3) mm(2)/s) in cancer and benign lesions were 0.84+/-0.19 and 1.58+/-0.36, respectively ($P<0.01$). The staging accuracy (superficial or deep myometrial invasion) was 94% for DWI and 88% for gadolinium-enhanced T1-weighted images. Coexisting adenomyosis and infiltrative myometrial invasion caused staging errors on gadolinium-enhanced T1-weighted images, whereas DWI could demonstrate the tumor extent correctly.[16]

Kido et al (2010) investigated the apparent diffusion coefficients (ADCs) of the uterine zonal structures (myometrium, endometrium and junctional zone) among reproductive women, and their changes during the menstrual cycle. Magnetic resonance (MR) images of seven healthy females (aged 24–31 years) were obtained during the periovulatory, luteal and menstrual phases. The average changes of ADC values (intraindividual ADC value variation) over three menstrual phases were 0.4161023 mm2 s 21 (range, 0.08–0.91) for myometrium, 0.5561023 mm2 s 21 (0.35–0.84) for endometrium, and 0.4061023 mm2 s 21 (0.18–0.59) for the junctional zone. The ADC values for myometrium and endometrium were lower in the menstrual phase, although there was some overlap of individual values. Interindividual variation in ADC value for a given zone or phase ranged from 0.4861023 mm2 s 21 to 0.8561023 mm2 s 21. Inter measurement variation between the two ROIs ranged from 0 to 0.4861023 mm2 s 21

per measurement. The magnitude of these variations was comparable to reported differences between malignant and non-malignant tissues.[1]

Fornasa et el [2012] evaluated the endometrial ADC values in 17 women measured on the fifth menstrual day, both at the fundus and at the isthmus of the uterus, were compared to the values obtained on the 14th day before the subsequent cycle. In 81 women (menstrual day: fifth through 21st) the endometrial ADC values measured at the fundus were compared to the values obtained at the isthmus of the uterus. The endometrial ADC values measured on the fifth day of the menstrual cycle were lower than those obtained in the periovulatory phase both at the fundus (mean 0.923 vs. 1.256 1023 mm2 /s) and at the isthmus (mean 1.297 vs. 1.529 1023 mm2 /s) of the uterus.[21]

Tsili et al [2016] conducted retrospective study included 194 women. The mean and SD (standard deviation) of ADC (×10−3 mm2 /s) of the endometrium was: menopause: 1.36 ± 0.18; menstrual phase: 1.24 ± 0.22; proliferative phase: 1.38 ± 0.20; and secretory phase: 1.50 ± 0. A wide variation of ADC of normal endometrium/myometrium was found between postmenopausal and reproductive age women. A standard reference of ADC of normal uterine zones is helpful, serving as a baseline when interpreting uterine diseases.[22]

Çavuşoğlu M et al [2016] enrolled 52 patients To investigate the feasibility of diffusion-weighted magnetic resonance imaging (DWI) with apparent diffusion coefficient (ADC) values in differentiating endometrial cancer from benign endometrial lesions in postmenopausal patients with vaginal bleeding and endometrial thickening and to predict the depth of myometrial invasion in endometrial cancer. : Fifty-two patients (mean age: 57 ± 10, range: 41–79) were enrolled in the study. Thirty-eight of the lesions were benign (27 as hyperplasia and endometritis; 11 as polyps). 14 of the 52 endometrial lesions were pathologically proven as cancers and underwent hysterectomy, and all the specimens were reported as endometrioid adenocarcinomas. The mean ADC value (10–3 mm2/second) of cancer (0.88 ± 0.10) was significantly lower than that

of benign lesions (1.78 ± 0.27, p = 0,001). There was no significant difference between ADC values of endometrial tissue in patients with FIGO stage 1A (0.87 ± 0.11, n = 9) and FIGO stage 1B (0.91 ± 0.07, n = 5). The staging accuracy was 92.9 per cent (13/14) for DWI and 85.7 per cent (12/14) for postcontrast T1-weighted images.[23]

Elsammak et al [2017] concluded that DW-MRI is useful in distinguishing malignant from benign endometrial lesions and tumor staging as well. Endometrial malignancies showed significant low ADC values (0.82 + 1.09 103 mm2 /s) compared to benign lesions (1.44 + 0.15 103 mm2 /s) (p: 0.000). Using 1.19 103 mm2 /s as cut-off value for distinguishing malignant from benign lesions achieved 88.9% sensitivity and 100% specificity.[17]

Mansour et al [2019] evaluate the role of DWI in the diagnosis and differential diagnosis of benign and malignant focal endometrial masses. The 50 studied lesions were classified according to their histopathological results into the benign group (28 lesions, 56%) and the malignant group (22 lesions, 44%). Conventional MRI could correctly diagnose 39 of the 50 lesions (22/28 benign and 17/22 malignant lesions), achieving a sensitivity of 77.27%, specificity of 78.56%, accuracy of 78%, predictive positive value (PPV) of 73.91%, and negative positive value (NPV) of 81.48%. By combining DWI and apparent diffusion coefficient (ADC) value mapping at a high b value (b = 1000) in MRI, we could correctly diagnose 47 of the 50 lesions (26/28 benign and 21/22 malignant lesions), with increased sensitivity (95.45%), specificity (92.86%), accuracy (94%), PPV (91.3%), and NPV (96%).[24]

6.3 AIMS AND OBJECTIVES OF THE STUDY

To assess the role of MR DWI with ADC values in characterisation of endometrium into normal and pathological (benign and malignant) endometrium, and to correlate with histopathological examination wherever possible.

7. MATERIALS AND METHODS

7.1 Source of Data

A prospective study will be done on all female patients referred for pelvic MRI to the Department of Radio-diagnosis, Dayanand Medical College and Hospital, Ludhiana over a period of 1 year from 1 March 2021 to 28 Feb 2022.

7.2 METHOD OF COLLECTION OF DATA

All female patients referred for pelvic MRI to the Department of Radio-diagnosis, Dayanand Medical College and Hospital, Ludhiana over a period of 1 year. Patients will be subjected to a multiplanar, multi sequential MRI scan of pelvis on a MAGNETOM SKYRA 48 Channel 3 Tesla MR Machine by Siemens, Germany. Written informed consent will be obtained from each patient and relevant detailed history will be elicited from all patients. Procedure will be explained to patient in his/her vernacular language to allay the fear and anxiety.

INCLUSION CRITERIA

All female patients undergoing pelvic MRI will be included in this study.

EXCLUSION CRITERIA

1. Patients in which ADC measurement is not possible due to thin endometrium or technical factors.
2. Pregnant Patients.
3. Patients who do not consent to be a part of the study.

MAGNETIC RESONANCE IMAGING PROTOCOL:

All patients will be undergo a multiplanar, multi sequential MRI scan of pelvis on a MAGNETOM SKYRA 48 Channel 3 Tesla MR Scanner by Siemens, Germany.

MR Imaging sequences will include T2 Weighted Sagittal, T2 Weighted Axial, T2 Weighted Coronal, T1 Axial Imaging and Diffusion-weighted.

Diffusion-weighted MR imaging in the axial plane of the uterus will be performed.

IMAGE ANALYSIS PROTOCOL

For diffusion weighted imaging: Signal intensity of the lesion will be assessed on high b-value diffusion weighted sequence.

For quantitative analysis: ADC values of the endometrium will be measured on the ADC map images by placing two regions of interest (ROI). We will measure two ROIs and use the average value, rather than just one ROI, to reduce random variability in the measurements.

MR SYSTEMS AND SCANNING METHOD

Sequences	**Localiser**	**T2 Sagittal**	**T1 Axial**	**T2 Axial**	**T1 Fat sat Axial**	**T2 Coronal**	**DWI**
Acquisition Time	0:25	3:29	2:55	2:47	3:25	2:44	3:22
Orientation	Trans versal	Sagittal	Axial	Axial	Axial	Coronal	Axial
Resolution Matrix	179 x 256	269 x 384	256 x 320	269 x 384	224 x 320	269 x 384	114 x 114
Number of Slices	9	25	25	25	25	25	25
FoV Read (mm)	420	230	220	220	220	230	220
FoV Phase (%)	100	100	100	100	100	100	100
Slice Thickness (mm)	7.0	3.0	3.0	3.0	3.0	3.0	3.0
Slice Gap (mm)	7.0	3.1	2.1	2.1	2.1	2.1	2.1
Repetition Time (msec)	1000	2800	680	3100	650	2800	4000
Echo Time (msec)	89	87	18	89	18	87	64
Flip Angle (deg)	160	180	154	180	154	175	-
Fat Suppression	None	None	None	None	Fat sat	None	SPAIR
Flow Compensation	No	No	Read	Slice	Read	No	-

DURATION OF STUDY

1 Year from 1 March 2021 to 28 Feb. 2022

OUTCOME: On the basis of ADC values endometrium will be classified as normal, benign (endometrial hyperplasia, endometrial polyp) and malignant (endometrial carcinoma) and their correlation with histopathology will be done wherever possible.

STATISTICAL ANALYSIS:

Data will be described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Sensitivity, specificity, positive and negative predictive values and accuracy of method and its confidence interval (95% CI) will be also calculated. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations will be done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

YES. The study is mainly based on investigations as Radiology itself is a tool of investigation. Interventions would be done as and when it is indicated alone. The study involves only humans. Informed consent would be taken after explaining about and before any procedure.

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached herewith

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PROFORMA

S. No

Date:

Name: Age/Sex:

MRD No.: Contact no.:

Address:

Co-Morbidity: 1) Diabetes 2) Hypertension 3) CAD 4) Others

History of : Carcinoma in Family Yes No

Hormone Replacement Therapy Yes No

LMP:

Menstrual Status: 1) Reproductive

2) Postmenopausal

Presenting Complaints:

1) Abnormal vaginal bleeding

2) Post-menopausal bleeding

3) Lower abdominal pain

4) Others

5) Incidentally detected (mode of detection)

Signature of Candidate

Signature of Supervisor

EXAMINATION

1)General Physical Examination:

2) Pelvic examination:

3) Lab Investigations:

- Hemogram

- RFTs

- Ultrasound Findings:

Signature of Candidate **Signature of Supervisor**

MRI FINDINGS

Endometrial Thickness:

DIFFUSION WEIGHTED IMAGES (DWI):

Signal intensity	Bright/ Dark
ADC value	

T1W IMAGING:

T2W IMAGING:

Histopathology (wherever done):

FINAL DIAGNOSIS:

Signature of Candidate **Signature of Supervisor**

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o..... .....am willing to participate in the study **"ROLE OF MR DIFFUSION WEIGHTED IMAGES(DWI) WITH APPARENT DIFFUSION COEFFICIENT(ADC) VALUES IN NORMAL AND PATHOLOGICAL ENDOMETRIUM"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

....

Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"ROLE OF MR DIFFUSION WEIGHTED IMAGES(DWI) WITH APPARENT DIFFUSION COEFFICIENT(ADC) VALUES IN NORMAL AND PATHOLOGICAL ENDOMETRIUM"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"ROLE OF MR DIFFUSION WEIGHTED IMAGES(DWI) WITH APPARENT DIFFUSION COEFFICIENT(ADC) VALUES IN NORMAL AND PATHOLOGICAL ENDOMETRIUM"ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

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ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਪਤਾ _____

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ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਪਤਾ _____

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ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

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ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ